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Clinical and Research Report 1985/86

87-02392

The Ontario Cancer Institute incorporating The Princess Margaret Hospital (OCI/PMH), is Canada's largest centre for cancer research, treatment and teaching. Since it opened in 1958, the OCI/PMH has earned an international reputation for excellence.

Each year approximately 7,000 new cancer patients are assessed and treated at this 202-bed University of Toronto teaching hospital. There are also more than 150,000 outpatient visits per year for evaluation, radiation therapy, chemotherapy and follow-up. On a rotating basis, the medical staff also travel to clinics in North Bay, Owen Sound, Peterborough, Sault Ste. Marie, Sudbury and Timmins to provide initial assessment and follow-up for patients in these regions.

At the beginning of this year, The Ontario Cancer Institute incorporating The Princess Margaret Hospital faced a critical crossroad.

Through the dedicated efforts of many, the year ended with the door finally opening on a vision for the future — commitment for funding a new research centre and hospital.

In this report, we present the results of that effort and the tradition of excellence which we know will continue in the decades to come.

Patient Care

Research

Education

The Ontario Cancer Institute incorporating The Princess Margaret Hospital
500 Sherbourne Street
Toronto, Ontario M4X 1K9

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1985-86
Opening The Door On A Vision For The Future

At the beginning of this past year, The Ontario Cancer Institute, which incorporates The Princess Margaret Hospital (OCI/PMH), reached a critical cross road. One road led to continued excellence in all fields of endeavour and the ability to care for large numbers of patients; while the other road led to continuing and increasing limitations for our oncologic role.

The year was highlighted by committment from the provincial government to completely rebuild and expand the Institute's patient care and research facilities. The Ministry of Health has promised $200 million to improve cancer services in Ontario. Of that, $133 million will go to OCI/PMH. An additional $50 million for the provincial program will be raised through a fund raising campaign which is currently being planned. The new OCI/PMH will continue to be associated with an acute care, university teaching hospital; and our objective in choosing a site will be to find a setting and environment which will be most supportive of *all* our patient care, research and teaching programs. Several sites are under consideration and discussions have taken place with the Ontario Cancer Treatment and Research Foundation, the University of Toronto and the teaching hospitals in Metro Toronto.

As Canada's largest cancer treatment and research centre, the OCI/PMH currently treats about 7,000 new patients per year and has about 26,000 on follow-up. In the research divisions, more than 30 career scientists affiliated with the University of Toronto conduct basic research in biology and physics.

This committment to fund a new centre has opened a door on a vision for the future. Months of planning and discussion are ahead and we expect the new centre will take eight to ten years to complete. But it has given us the confidence to proceed with planning a centre which will be on the leading edge — a centre which will enhance the high quality of patient care, research and teaching carried out by our staff. This report reflects the diversity of achievement of our staff and the tradition of innovation and excellence they have established.

Raymond Bush

R.S. Bush
Director

Members of the Board and Staff

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Mr. F. Udell
Mr. J.B. Vaughan ****

1985-86

* *New Appointment*
** *Retirement Resignation*
*** *Deceased*
**** *Honorary Member*

MEDICAL, SCIENTIFIC AND ADMINISTRATIVE STAFF

Director: R.S. Bush, M.D.

Clinical Services

R.E. Alison, M.D.
F.A. Beale, M.B.
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Chief, Department of Dental Services
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H.A. Messner, M.D.
N. Miller, M.D. *
M.D. Minden, M.D.
B. O'Sullivan, M.B. *
B.J. Patterson, M.D.
D.G. Payne, M.D.
M.E. Platts, M.D.
P.Y.C. Poon, M.B.
J.F. Pringle, M.B.
I.C. Quirt, M.D.
G.A. Rawlings, M.D.
D.F. Rideout, M.B.
Chief, Department of Diagnostic Radiology
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G.M. Thomas, M.D.
T. Treger, M.D.
P.G. Tuffnell, M.D.
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D. Warr, M.D.
J.L. Yeoh, M.D.

Biological Research

Head:
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A. Bernstein, Ph.D. **
R.N. Buick, Ph.D.
A. Ciampi, Ph.D. **
A.J. Cunningham, Ph.D.
R. Gronostajski, Ph.D. *
R.M. Gorczynski, Ph.D.
N. Hozumi, M.D., D.M.Sc. **
V. Ling, Ph.D.
H. Llewellyn-Thomas, Ph.D. *
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S. Minkin, Ph.D. *
N. Miyamoto, Ph.D. *
R.A. Phillips, Ph.D. **
J.E. Till, Ph.D.
D. Tritchler, Sc.D.

Physics

Head:
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M. Bronskill, Ph.D.
J.R. Cunningham, Ph.D.
G. DeBoer, Ph.D.
A. Fenster, Ph.D.
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R.P. Hill, Ph.D.
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M. Yaffe, Ph.D.

Honorary Staff

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Assistant Administrators:
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AUXILIARY OF THE PRINCESS MARGARET HOSPITAL AND LODGE

President:
Mrs. E. Sauro

Biological Research & Physics Divisions (From the Dept. of Medical Biophysics, University of Toronto and resident at OCI/PMH)

Postdoctoral Fellows
P. Benveniste, M.D.
C. Birek, D.D.S., Ph.D.

Residents, Fellows, Graduate Students

L. Boux, Ph.D.
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G. Chen, M.D.
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J. Filmus, Ph.D.
G. Fulop, Ph.D.
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K. Laderoute, Ph.D.
C. Luk, Ph.D.
C. Magli, Ph.D.
B. McParland, Ph.D.
J. Milligan, Ph.D.
J. Miyamuchi, M.D.
H. Pircher, Ph.D.
M. Reis, M.D.
B. Rovinski, Ph.D.
B. Toyonaga, Ph.D.
Y. Yoshikai, M.D.
P. Zucker, Ph.D.

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D. Arlen, B.Sc.
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C. Caldwell, M.Sc.
N. Cardinal, M.Sc.
L. Catz-Biro, B.Sc.
A. Crawley, B.Sc.
I. Cunningham, M.Sc.
L. Dafoe, M.Sc.
K. Deuchars, M.Sc.
A. Dulhanty, B.Sc.
J. Endicott, B.Sc.
A. Goddard, B.Sc.
K. Graham, M.Sc.
B. Gunhouse, B.Sc.
P. Hardy, M.Sc.
P. Johns, M.Sc.
N. Kartner, M.Sc.
A. Kerr, M.Sc.
B. Korycka, B.Sc.
R. Kroeker, B.Sc.
G. Lockwood, B.Sc.
K. Mah, M.Sc.
R. Marshall, M.Sc.
E. McVeigh, B.Sc.
P. Munro, M.Sc.
D. Munroe, M.Sc.
C. Newcomb, M.Sc.
W. Ng, B.Sc.
B. Nishikawa, M.Sc.
T. Nguyen, B.Sc.
D. Rotin, M.Sc.
R. Sangster, M.Sc.
G. Santyr, B.Sc.
S. Sharkey, B.Sc.
M. Sherar, B.Sc.
J. Squire, M.Sc.
J. VanHeteren, M.Sc.
M. Weinberg, B.Sc.
M. Woo, M.Sc.
M. Wood, Ph.D.
D-D. Wu, M.D.
S. Yamada, M.Sc.
M. Yoshimura, M.Sc.
S. Young, M.Sc.
A. Yu, B.Sc.
M. Zabal, B.Sc.

■ Clinical Services

(The following were at OCI/PMH for varying periods July 1/85-June 30/86)

Department of Radiation Oncology
Residents
Dr. M. Aref
Dr. R. Bissett
Dr. J. Bowen
Dr. M. Brundage
Dr. P. Chabot
Dr. F. Ferris
Dr. A. Fyles
Dr. K. Goddard
Dr. F. Karsan
Dr. F-F Liu
Dr. L. Machul
Dr. F. Perera
Dr. J. Radwan
Dr. D. Rheaume
Dr. C. Theriault
Dr. A. Thornton
Dr. R. Tsang
Dr. P. Warde

Fellows
Dr. M. Guizzardi (Exchange Visitor)
Dr. P. Davey

Clinical Assistants
Dr. J. Crook
Dr. B Esche
Dr. C-S Wong

Resident Electives
Dr. P. Shuen (Gynae/Oncology)
Dr. M. Bertrand (Gynae/Oncology)
Dr. A. Porter (Cross Cancer Inst.)
Dr. M. Periera (Kingston Cancer Clinic)
Dr. R. Gramatovici (Kingston Cancer Clinic)

Department of Medicine
Medical Oncology Residents
Dr. D. Ajarim
Dr. E. Chouinard
Dr. R. Haq
Dr. R. MacCormick
Dr. U. Sagman
Dr. J. Slingerland
Dr. M. Trudeau
Dr. T. Vuong
Dr. T. Whelan

Pharmacology Oncology Residents
Dr. M. Moore

Haematology Residents
Dr. K. Almomen
Dr. H. Sutherland
Dr. L. Larratt

Clinical Fellows
Dr. A. Boutan-Laroze
Dr. Pl. Clingan
Dr. P. Goodwin
Dr. L. Kaizer
Dr. E. Haron (Exchange Visitor)
Dr. P. Ruffie (Exch. Visitor)
Dr. T. Wang (Exch. Visitor)

Research Fellows
Dr. M. Friedlander
Dr. J. Zalcberg

Department of Nuclear Medicine
Clinical Fellows
Dr. R. McLean
Dr. R. Loncar (Exchange Visitor)

Department of Diagnostic Radiology
Clinical Fellows
Dr. H. Dunlap

Department of Ophthalmology
Clinical Assistant
Dr. A. Drysdale

Department of Pathology
Residents
Dr. M. Fearon
Dr. J. Hart
Dr. R. Hegele
Dr. G. Kainth
Dr. P. Shokry

Neuropathology
Dr. E. Consky

Orthopaedic
Dr. T. Love
Dr. N. Ogston
Dr. J. Wright
Dr. J. McMahon

Awards and Honours

Bush, RS.
Elis Berven Lecturer, Swedish Medical Association. Stockholm, Sweden, November, 1985.

Bush, RS.
Honorary Membership, European Society for Therapeutic Radiology and Oncology. Stockholm, Sweden, June, 1985.

Gannon, MT.
Burroughs Wellcome Award in Recognition of Outstanding Contribution to the Profession of Hospital Pharmacy. Toronto, 1986.

Gannon, MT.
Best poster presentation award at the annual Federation of International Pharmacists Symposium. Montreal, Quebec, 1985.

Mak, TW.
Presidential Lecturer, American Society of Hematology Annual Meeting, 1985.

Mak, TW.
Keynote Address, Japanese Biochemical Society Annual Meeting, 1985.

Mak, TW.
Merit Award, Federation of Chinese Professionals of Canada, 1985.

Mak, TW.
Steacie Prize, Steacie Trust Foundation, 1986.

Mak, TW.
Honorary Professor, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China, 1986.

Mak, TW.
Honorary Professor, Beijing Union Medical University, Beijing, China, 1986.

Mak, TW.
Distinguished Lecturer, University of Rochester, 1986.

Mak, TW.
Pfizer Lecturer, Clinical Research Institute of Montreal, 1986.

Ottensmeyer, P.
Citation of Merit, Canadian Cancer Society, March 1986.

Rawlinson, JA, Galbraith, DM, Munro, P.
Farrington Daniels Award for best article on Radiation Dosimetry. Awarded by the American Association of Physicists in Medicine, 1985.

Simpson, W.J.K.
Visiting Professor. University of Bogota, Columbia, February 1985.

Dr. Tak Mak, a senior scientist in the Biology Division, has received many international awards during the past year for his work on T-cell receptors.

Miss Mary Gannon, department head in Pharmacy, received the Burroughs Wellcome Award in recognition of her contributions as a pharmacist on a research project. The project evaluated the usefulness of a urinary assay for monitoring exposure to chemotherapeutic agents handled by health care workers. She is shown discussing the results with the chief investigator, Dr. Peter Tuffnell, Chief of Microbiology.

Clinical Oncology

Clinical Programs and Research

The Lymphoma Program

Approximately 460 patients with malignant lymphoma are annually referred to The Princess Margaret Hospital. Of this total, approximately 100 patients are referred solely for consultative opinions or short term management. The remaining 360 patients receive active management and follow up; by diagnosis this group consists of approximately 90 patients with Hodgkin's Disease, 180 patients with non-Hodgkin's lymphoma and 90 patients have multiple myeloma. The core components of the Lymphoma Program are a data management system, a coordinated policy of disease investigation and treatment, and a clinical research interface to promote study of lymphoma cell biology.

■ *Lymphoma Data Management*

Susan Brooks, C.H.H.R.A.(c), Health Records Administrator, Medical Records
Dona Seto, Health Records Technician, Medical Records
A. Byrd, M.Sc, Programmer/Analyst, Computer Services
G. DeBoer, Ph.D., Head, Department of Biostatistics
S.B. Sutcliffe, M.D., Radiation Oncologist/Senior Scientist

The data management system was designed to provide an accurate, current account of lymphoma practice at The Princess Margaret Hospital.

The system comprises two sections; a "forms-oriented" basic data entry and retrieval system, and an analysis system involving DATATRIEVE (D.E.C.) and other statistical packages.

Biographies, therapy and follow-up files are entered on all patients with malignant lymphoma referred to PMH for management within 6 months of initial diagnosis and/or therapy. In addition to ongoing analysis of treatment results, modifications to provide prospective identification of clinic attendance and scheduled investigations, and edit checks to ensure the validity of entered data, are being incorporated into the system. Common usage of the database by the participating institutions in Metropolitan Toronto is under development.

Clinic Staff

Radiation Oncologists
H. Bean, M.D.
R.M. Clark, M.B.
A. Dembo, M.B.
P. Fitzpatrick, M.B.
M. Gospodarowicz, M.D.
S.B. Sutcliffe, M.B.
Medical Oncologists
R. Alison, M.D.
D. Bergsagel, M.D.
J. Curtis, M.D.
R. Hasselback, M.D.
J. Meharchand, M.D.
I. Quirt, M.D.
J. Sturgeon, M.B.
T. Chua, Biostatistics
D.F. Rideout, M.B., Chief, Imaging Department

Hodgkin's Disease

Following a detailed retrospective analysis of outcome following radiation therapy for clinical stage I and II Hodgkin's disease for the period 1968-1977, guidelines for investigation and treatment of localized disease were developed. The management strategy was based upon identification of clinical and histopathological attributes of established independent prognostic value at presentation[1]. A prospective application of these guidelines to determine the optimal role of radiation therapy and combined modality therapy for patients with localized disease is ongoing, and comparison of results with those of centers employing routine surgical staging may clarify the role of laparotomy in standard management of early Hodgkin's Disease.

Members of the Lymphoma Group collaborated in the development of the N.C.I.(C) Hodgkin's Disease IV Study and contribute patients to its accrual. This study compares two forms of alternating sequence chemotherapy for patients with Stage IIIb and IV disease with the intention of defining the most effective and least toxic therapy for this patient population.

Non-Hodgkin's Lymphoma

The experience with management of localized non-Hodgkin's lymphoma with radiation therapy has been analyzed for the period 1967-1978[2]. In addition, analyses of outcome following radiation therapy for specific extranodal presentations of localized lymphoma have been undertaken. Guidelines for the management of patients with localized non-Hodgkin's lymphoma involving nodal and extranodal sites according to multiparameter prognostic groups are under development. This approach should define the optimal role of radiation in localized non-Hodgkin's lymphoma and permit evaluation of chemotherapy with or without radiation in patients with localized disease who are at high risk for relapse.

Participation in the N.C.I.(C) LY-3 study to define the importance of adriamycin dose in an intensive combination chemotherapy protocol (B.A.C.O.P.) for patients with advanced high grade lymphoma continues.

Patients are also entered into N.C.I.(C)-sponsored Phase 2 studies of investigational new drugs in patients with recurrent or refractory non-Hodgkin's lymphoma. A study of spirogermanium has been completed and two new agents, acivicin and menagarol, are currently under investigation.

Plasma Cell Myeloma

Four trials of treatment for myeloma in cooperation with the National Cancer Institute of Canada Clinical Trials Group have been completed.

a) Melphalan And Prednisone Combination

The MY-1 trial tested the value of melphalan and prednisone (MP) *versus* combination of melphalan, cyclophsophamide, carmustine and prednisone administered either sequentially or concurrently. MP was just as effective as the drug combination in inducing responses and prolonging survival. A surprising finding was the increased incidence of acute leukemia in myeloma patients treated with alkylating agents. Continued observation of this large group of 359 patients to 10 years has shown that the actuarial risk of developing acute leukemia was greatest during the first 50 months and has continued to rise to reach 26 percent at 10 years[3].

b) Maintenance Therapy With MP

The MY-2 trial tested the value of maintenance therapy with MP. Maintenance of MP did prolong the duration of the first remission. However, patients who relapsed on no maintenance therapy usually responded again to renewed MP. When the duration of the first and subsequent remissions was added, no significant difference between the total duration of remission for the maintenance and no maintenance groups was found. Also, there was no difference in overall survival. Patients on MP maintenance therapy received a much larger total dose of melphalan than those in the no maintenance arm. The fact that the incidence of acute leukemia is very similar in the maintenance and no maintenance groups suggests that the total dose of melphalan is not an important risk factor in the development of acute leukemia[4].

c) Treating Resistance To MP

In the MY-3 trial, the value of weekly cyclophosphamide (250 mg/M^2) and alternate day prednisone as secondary treatment for patients who were resistant to MP was tested. This regimen was well-tolerated and resulted in objective responses in 7 of 28 (25 percent) of patients who had never achieved a stable response on MP (primary resistance) and in 10 of 29 (35 percent) of those who had responded to MP and then progressed despite continued therapy (secondary resistance). It was concluded that weekly cyclophosphamide and alternate day prednisone is a useful form of second line treatment.

d) Didronel For Skeleton Maintenance

The MY-4 trial was designed to test the value of a diphosphonate (Didronel) in maintaining the skeleton in myeloma patients. Osteolytic lesions causing fractures and generalized osteoporosis leading to vertebral collapse, are major complications in this disease. All patients are treated with MP and randomized to receive didronel or a placebo. Over 153 patients have been entered on this study and patient registration will soon be complete. In the analysis, changes in height, bone pain, pathologic fractures, vertebral collapse, the incidence of hypercalcemia and the survival of the two groups will be compared.

e) Interferon And Patients Treated With MP

The design of the MY-6 trial has been completed, in which the effectiveness of interferon in maintaining remissions and prolonging the survival of myeloma patients treated with MP will be tested.

■ *The Research Program*

S. Benchimol, Ph.D., Senior Scientist, Biological Research Division
T.C. Brown, M.D., Chief, Department of Pathology
T. Mak, Ph.D., Senior Scientist, Biological Research Division
E.A. McCulloch, M.D., Head, Biological Research Division
H. Messner, M.D., Medical Oncologist/Senior Scientist
R. Miller, Ph.D., Senior Scientist, Biological Research Division
M. Minden, M.D., Medical Oncologist/Senior Scientist
B. Patterson, M.D., Pathologist
I. Quirt, M.D., Medical Oncologist
S.B. Sutcliffe, M.D., Radiation Oncologist/Senior Scientist

Y.C. Dai, Visiting Professor, Jaingxi Institute of Medical Sciences, China
M. Friedlander, M.D.,Ph.D., Clinical Fellow, Department of Medicine
H. Greisser, Postdoctoral Fellow, Kiel, Germany
B. Lim, M.D., Research Fellow, Institute of Medical Science, University of Toronto
A. Nguyen, Medical Student, University of Toronto
M. Tweeddale, M.D., Research Fellow, Biological Research Division
J. Zalcberg, M.D., Ph.D.,Clinical Fellow, Department of Medicine

D. Booth, R.R., Senior Laboratory Technologist
S. Eakins, R.T., Laboratory Technologist
E. Ehman, B.Sc., Senior Technician, Division of Biological Research
N. Jamal, Senior Technician, Division of Biological Research
G. Smith, R.T., Senior Laboratory Technologist

The Lymphoma Phenotyping Laboratory (Smith, Booth, Mason, Eakins, Brown, Miller, Ehman, McCulloch, Quirt, Patterson, Sutcliffe)

This laboratory has been developed to integrate the standard histopathological evaluation of lymphoma cells utilizing the techniques of flow cytometric analysis of surface phenotype and determination of ploidy and DNA distribution in fresh and fixed material. The independent prognostic value of functional characteristics of lymphoma cells may be explored given standardization of treatment options, however it is recognised that as a tertiary referral centre, patients undergoing functional characterization of biopsy material may represent a minority of the population receiving therapy at PMH.

The centralized receipt and processing of material within the Phenotyping Laboratory has facilitated the development of two other research programs.

The Use Of Molecular Probes To Identify Clonal Populations And The Identification Of Aberrant Gene Rearrangements In Lymphoma Cell Populations (Zalcberg, Friedlander, Minden, Messner, Tweeddale, Mak, Greisser)

Molecular probes to demonstrate rearrangement of genes for immunoglobulin and the T-cell receptor have shown a high degree of correlation with surface phenotype analysis. In several biopsy specimens, probes to detect gene rearrangement have defined a clonal population comprising a minor component of the total cell population thereby clarifying ambiguities inherent in surface phenotype profiles. The general utility of immunoglobulin gene/T-cell receptor gene rearrangement for classification of lymphoid malignancies has thus been confirmed.

This technology has also permitted the identification of bi-clonal disease ie. discordant rearrangement in geographically or temporally unrelated biopsy specimens from the same individual. The issue of inherent susceptibility to more than one type of lymphoid malignancy or the evolution of separate clones from one common progenitor cell is thereby raised and will form the basis of further investigation.

Cytogenetic analysis has demonstrated certain characteristic translocations associated with malignant lymphoma. The region of the alpha chain locus of the T-cell receptor is frequently involved in chromosome translocations in T-cell malignancies[5-8]. In two patients studied, the alpha chain was split by such a translocation[9]. Attempts to isolate the rearranged pieces of DNA to determine the relationship of translocation to the development of the malignant state are on-going[10].

Cell Culture Examination In Patients With Malignant Lymphoma (Tweeddale, Messner, Lim, Jamal, Benchimol, Minden, Zalcberg, Nguyen, Dai)

a) *Development of a culture system for clonogenic precursors*

A culture system for lymphoma and myeloma cells has been developed to identify growth characteristics that define patients at high risk for early death with standard therapy Prolonged culture has been achieved with cell suspensions from patients with high grade lymphomas, and subsequent review has demonstrated a strong correlation between sustained growth *in vitro* and poor clinical outcome[11].

The demonstration that *in vitro* growth characteristics following initial biopsy predict failure on standard therapy, may provide a basis for selection of high risk patients for novel treatment approaches.

b) *Evaluation of cell cultures from patients with lymphoma*

Detailed study of cell cultures have indicated that:

- Growth patterns from patients with high grade lymphoma are heterogeneous.
- The majority of cultures do not require ancillary growth factors for sustained proliferation.
- Cultures demonstrating autonomous growth may replace the need for exogenous growth factors in cultures that would otherwise fail to exhibit sustained proliferation.
- Lymphoma cell colonies can be propagated as cell lines with retention of stable phenotype. In a small number of cases where chromosomal abnormalities have been defined, an aberrant gene rearrangement has been detected.
- Cultures demonstrating sustained growth have high levels of P-53 protein.
- Immunoglobulin gene rearrangement studies of cells from primary tumor samples and their respective cell lines indicate identical rearrangement patterns, thereby providing direct evidence that cells grown in culture are derived from the tumor cell population.
- Cell lines are being used to test the efficiency of various purging methods such as:
- monoclonal antibody & compliment
- monoclonal antibody coupled to immunotoxin
- light sensitizers

These approaches might be useful for future development in autologous bone marrow transplantation.

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Breast Cancer

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During the past year 1,435 new patients with breast cancer plus follow-ups have been seen by this group. In addition, 122 new patients and 469 follow-ups were seen in the breast diagnostic clinic. These numbers continue to increase significantly with the advent of new studies.

We are actively involved in studies assessing the value of adjuvant hormone and chemotherapy and also conservative treatment.

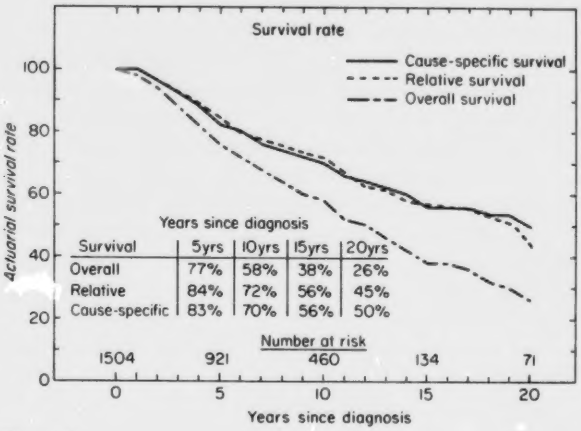
Our Institute has pioneered the concept of breast conservation since it opened in 1958. This method of treatment has been gathering momentum in recent years resulting in the referral of many more patients with early breast cancer who previously would not have been referred to this hospital. These patients are treated surgically by partial mastectomy ("lumpectomy") and axillary dissection. This is now becoming the primary surgical treatment choice for operable breast cancer.

It is now accepted that irradiation of the regional nodes may reduce local recurrence but does not improve survival. The trend is now to irradiate only the breast after partial mastectomy and axillary dissection, or in some instances to recommend careful follow-up with no radiation. Many patients are also referred for palliative treatment after the development of metastatic disease. Hormone and chemotherapy studies are also available for these patients. Palliative irradiation for metastatic disease forms a large component of the work in the Department of Radiation Oncology. As breast cancer is a very common disease, the workload is heavy and exacting. It is also a capricious disease and patients may live for many useful years even in the presence of active disease. This, therefore, creates a very large number of patients requiring continual long term follow-up. Working groups have been developed in the Departments of Medicine and Radiation Oncology and the two groups meet frequently to discuss the progress of studies and plan future treatment policies. Studies are carried out in cooperation with the Toronto Breast Group and the new Ontario Clinical Oncology Group in association with the University teaching hospitals.

Patients are followed, not only at The Princess Margaret Hospital but also in all the peripheral clinics. The group is assisted by the following clinical trials nurses: B. Sinclair-Murray, M. Clark, T. Baskerville, C. Mayers and G. Larocque.

Conservation Therapy — Retrospective Study

From 1958 until 1964 we accumulated a total of 1,504 patients who were treated by partial mastectomy prior to referral to The Princess Margaret Hospital. None of the patients included in this study had clinical evidence of regional nodal involvement. Following partial mastectomy, most of the earlier patients received postoperative irradiation to the breast and regional nodes but more recently 374 patients were treated by excision only, with no irradiation and 662 received radiation therapy only to the breast. Patients were excluded from analysis if adjuvant therapy had been given, to avoid bias. The overall actuarial survival of this group at five years



Survival	5yrs	10yrs	15yrs	20yrs
Overall	77%	58%	38%	26%
Relative	84%	72%	56%	45%
Cause-specific	83%	70%	56%	50%

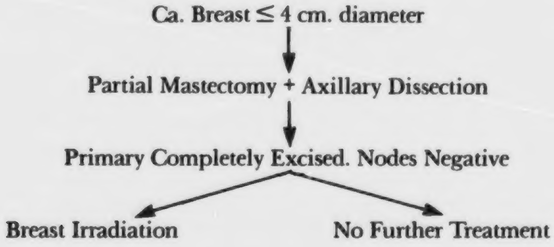
Figure 1.

was 77% and at 10 years 58%. The relative survivals were 84 and 72% respectively (Figure 1). There was no difference in survival whether radiation was given or not. Patients treated by partial mastectomy with no other treatment had the same survival at 10 years as those who were irradiated. The breast relapse rate was undoubtedly higher in the unirradiated group but this did not appear to be detrimental to survival. The survival of this group of patients therefore compares favorably with reported survival rates for radical surgery.

Conservation Therapy — Prospective Study

As a result of the retrospective study, we have commenced an Ontario wide prospective study as outlined here:

Ontario Clinical Oncology Group Study


Ca. Breast ≤ 4 cm. diameter
Partial Mastectomy + Axillary Dissection
Primary Completely Excised. Nodes Negative
Breast Irradiation
No Further Treatment

With strict surgical radiotherapeutic and pathological control, we hope to be able to define more accurately those patients who may or may not require postoperative irradiation. Dr. R.M. Clark (OCI) and Dr. P.B.M. McCullough (OCTRF) are co-principal investigators and the study is supported by the Ontario Clinical Oncology Group (OCOG). Centres participating in this study are: Ontario Cancer Institute, Ottawa General, Ottawa Civic, Hamilton, Thunder Bay and Windsor. In addition we are now pleased to welcome The London Clinic as a new participant.

Approximately 400 patients have been entered into the study to date. We hope to achieve the final target of 800 patients within the next two years.

Gastrointestinal Oncology

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During the past year the group has continued to study combined radiation and chemotherapy protocols for epidermoid cancers of the esophagus and anal region, adjuvant radiation therapy for adenocarcinoma of the rectum, and chemotherapy for metastatic colorectal cancer.

Metastatic Adenocarcinoma Of The Colon And Rectum

Dr. Fine and Dr. Erlichman, in collaboration with Dr. A. Wong of the Tom Baker Cancer Centre in Calgary, Alberta, have completed a randomized Phase III trial for patients with metastatic adenocarcinoma of the rectum. The patients were treated with either 5-Fluorouracil or with high dose folinic acid and 5-Fluorouracil.

The early evaluation of this trial showed a higher response rate for those who received folinic acid and 5-Fluorouracil, but data on the duration of response is not yet complete. This combination of agents will be tested against other gastrointestinal adenocarcinomas over the next year.

Adenocarcinoma Of The Rectum

Although surgical resection remains the standard therapy for rectal adenocarcinoma, a small number of patients are either medically unfit for major surgery, or refuse procedures which require a colostomy.

The group has recently analyzed the results of radical external beam radiation therapy in these patients. The effectiveness of radiation in controlling a proportion of the tumors in these patients, an observation previously reported by Rider[1], has been confirmed.

Between 1958 and 1977, 144 patients were treated by radiation, usually to doses of 45-50 Gy in 4 weeks. Local control was obtained in 39 per cent (242 of 61) of those with mobile tumors[2].

The overall 5-year uncorrected survival rate was 22 per cent, reflecting the generally older age of the patients treated in this way. For the patient with a mobile rectal cancer who is unable to undergo surgery, radiation therapy offers a reasonable prospect for local control. Fixed tumors are more difficult to control, and current programs are evaluating combined radiation and resection for these patients.

A randomized trial has been opened in collaboration with a number of surgeons from the University of Toronto and in areas served by OCI/PMH, to evaluate adjuvant radiation therapy in patients with operable adenocarcinoma of the rectum. In this study the outcome of treatment by surgical resection alone is being compared with resection preceded by pelvic radiation to 45 Gy in 5 weeks.

Carcinoma Of The Anal Canal

We have continued our clinical studies of the combination of concurrent chemotherapy and radiation therapy for epidermoid carcinoma of the anal canal. The high overall control rate of about 85 per cent for the primary cancer has been maintained. In the past year we have analyzed the role of elective radiation of the inguinal lymph nodes in patients with anal cancer. If the nodes are not treated, about 15 per cent to 25 per cent of patients develop metastases in this region even though their primary cancer may remain under control. Most surgical authorities do not recommend elective dissection of these nodes, because of the significant side effects which may follow dissection and because of the relatively small numbers of patients who might benefit from the surgery. In a retrospective analysis of the patients treated at the PMH with radiation therapy, we found that 18 per cent (6 of 33) developed tumor recurrence in the inguinal region if the nodes had not been irradiated, but only 3 per cent (2 of 79) failed in the groin when the radiation fields had covered this area. The morbidity from the radiation was slight, and we now include these node areas electively in the radiation fields when patients with anal cancer carcinoma are treated.

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Neuroendocrine Group

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M.E. Platts, M.D. Neuropathologist
W.J. Simpson, M.D., Radiation Oncologist
S.B. Sutcliffe, M.B., Radiation Oncologist
J. Van Dyk, M.Sc. Clinical Physicist

Over the past year, members of the Neuroendocrine Group have participated in the weekly meetings of Toronto endocrinologists and of Wellesley/PMH neuroscientists, have been involved in the undergraduate syllabus for endocrinology, and the postgraduate training program for endocrinology. Drs. Gospodarowicz, Simpson and Sutcliffe conduct a biweekly teaching session for residents based on new patients referred to the Endocrine Clinic, and have instituted a new monthly conference on endocrine tumors for Toronto endocrinologists, head and neck surgeons and neurosurgeons. They also contributed a chapter on thyroid cancer for Moss and Cox's sixth edition of *Radiation Oncology: Rationale, Technique and Results.*[1]

Thyroid Cancer

The ongoing analysis of data from the Canadian Survey of Thyroid Cancer[2] has identified nine prognostic factors for patients with papillary and follicular thyroid cancer: post-operative status, (Figure 1) age at diagnosis, (Figure 2) extra-thyroidal invasion, distant metastases, nodal involvement, differentiation, sex, primary tumor size and pathology (descending order of importance). This review also defined more clearly the relative and complementary roles of radioiodine and external radiation both as adjuvant therapy and in the treatment of unresectable or metastatic disease. Further analyses will involve medullary and anaplastic thyroid cancers.

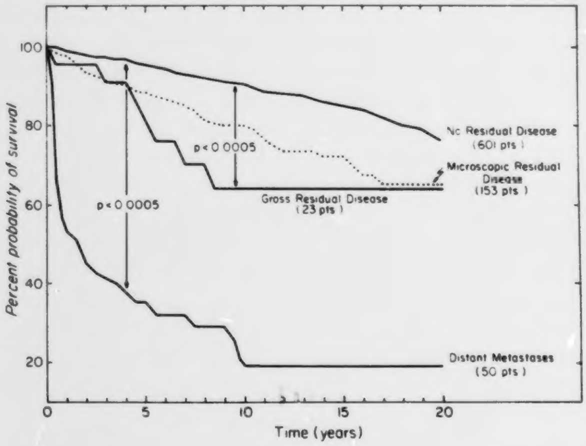

Figure 1. Papillary thyroid cancer: influence of post-operative status on overall survival.

The optimum management of thyroid cancer has never been studied by randomized prospective clinical trials. For the past five years, the Thyroid Cancer Treatment Cooperative Study Group, led by Dr. Leslie DeGroot (University of Chi-

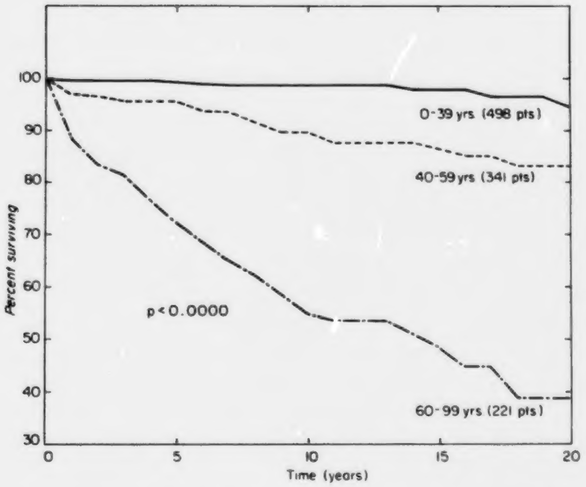

Figure 2. Papillary thyroid cancer: influence of age on cause-specific survival.

cago) has worked hard to produce six protocols involving studies of both differentiated and anaplastic cancers. Dr. Simpson has been a member of the Executive Committee and chairman of the Radiotherapy Subcommittee, Dr. Sutcliffe has been a member of the Chemotherapy Subcommittee, and Dr. Carruthers has been a Review Pathologist for the Group. In 1985, the N.C.I. (U.S.) approved the studies but gave a priority rating insufficient to obtain funding. Unless alternate funding can be obtained, these valuable trials will not be implemented.

Metastatic medullary thyroid carcinoma is usually accompanied by profuse watery diarrhea, which is debilitating and difficult to control. In 1985, Dr. Uri Sagman (Fellow in Medical Oncology) was asked to treat such a patient with a somatostatin analogue, which he had used successfully in a symptomatic patient with metastatic carcinoid tumor. Although tumor shrinkage was not observed, symptomatic relief was obtained. Dr. Sutcliffe has continued his search for a more effective chemotherapeutic regimen for patients with metastatic medullary cancer than the DTIC-Adriamycin combination which, although effective, is limited by its toxicity.

Medullary thyroid cancer is familial in approximately 25% of newly diagnosed patients. The screening of relatives continues in the PMH Medullary Screening Clinic, using the pentagastrin-stimulated calcitonin test. Since 1976, more that 200 relatives have been tested, and 20 have undergone a thyroidectomy because of hypercalcitonaemia. Six were found to have medullary cancers (0.3 - 1 cm diameter); 12 had its benign precursor, C-cell hyperplasia; one had lymphocytic thyroiditis; and one had no thyroid abnormality histologically. An example of a kinship with familial medullary cancer of the thyroid gland is shown in Figure 3.

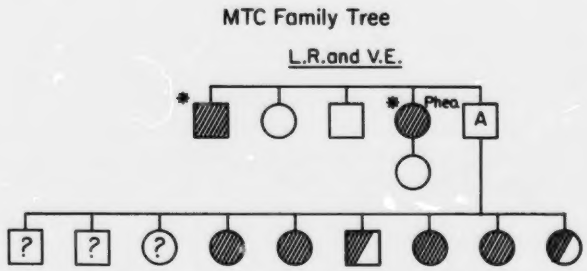

Figure 3. Schematic example of a kinship with familial medullary carcinoma of the thyroid gland. (circles = females; squares = males; cross-hatched = medullary cancer; half-hatched = C-cell hyperplasia; clear = normal; ? = not tested)

The control of anaplastic thyroid cancer remains elusive: only 10% of these patients survive two years. Following an enthusiastic report from Memorial Hospital, New York, we followed their regimen of hyperfractionated radiation with concurrent low-dose Adriamycin. After encountering severe toxicity without local tumor control in seven consecutive patients, this approach has been abandoned. We are now discussing a protocol involving hyperfractionated split-course radiotherapy plus chemotherapy, with surgical resection mid-way through the radiation if that appears to be technically possible.

In our re-evaluation of the treatment of anaplastic (or other bulky unresectable thyroid cancers), we asked Mr. Van Dyk to help us design a radiotherapeutic technique which would permit the delivery of a very high dose to a large tumor volume which includes posterior cervical lymph nodes, without exceeding spinal cord tolerance. The result is shown in the accompanying figure: (Figure 4) a split-field high energy photon radiation beam anteriorly and posteriorly combined with a central anterior electron beam of appropriate energy to spare the spinal cord. Unfortunately, the heavy pressure on our high energy machines has precluded the use of this technique in most anaplastic thyroid cancer patients, in whom

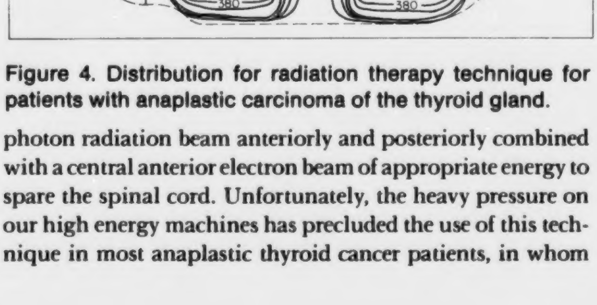

Figure 4. Distribution for radiation therapy technique for patients with anaplastic carcinoma of the thyroid gland.

treatment must be started within several days because of their rapid growth.

Pituitary Adenomas

Pituitary adenomas are benign tumors which are often treated with radiotherapy. However, their clinical course is not well documented, especially regarding recurrence rates, and particularly since the advent of microsurgery and bromocryptine. Accordingly, we are proposing a Toronto Pituitary Register, which will record prospectively all patients from the Toronto area, in an attempt to determine prognostic factors and the impact of the various treatment modalities.

Comparison of CT and MR

The neuroendocrine group has been interested in comparing CT and MR in the anatomic demonstration of pituitary tumors and tumors of the brain stem, posterior fossa and spinal cord. At this point, it appears that MR is superior in most, but not all, instances. Comparison of the two methods will have to continue when both types of equipment are upgraded in the coming year.

Glioblastoma Multiforme

Glioblastoma multiforme is a lethal brain tumor which, unfortunately, is the commonest tumor arising in the central nervous system. The median survival is ten months, and few patients survive 5 years. Death is due to our inability to eradicate the primary tumor, and not due to distant metastases. One novel approach is to greatly increase the radiation dose by carrying out a radioactive implant of the tumor following partial resection. Dr. Laperriere has developed a protocol for the randomized prospective study of patients treated by surgery and external radiation, compared to surgery, external radiation and a radioactive implant. An essential part of this protocol is the development and testing of the measurement of "quality of life" in brain tumor patients, in collaboration with Dr. Norman Boyd, P.M.H., Department of Medicine. A radiation neurotoxicity scoring system will also be tested.

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Dermatologic Oncology

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Following the regular weekly clinic a conference is held when both new patients and problem cases are discussed. Everyone benefits from these multidisciplinary discussions where the various treatment options are reviewed. All of the senior staff representing radiation oncology, dermatology and surgery attend, together with PMH residents and others from the departments of general practice, surgery and dermatology. Once a month a cross-Toronto Tumor Board is held and attended by other specialists from the teaching hospitals who have an interest in dermatological oncology. Here, patients with specific problems are reviewed and multidisciplinary consensus on management is recommended. In addition, staff review aspects of practice and this eventually leads to the development of treatment policies. Residents are encouraged to perform small studies and to deliver a five minute paper.

Current retrospective studies include a review of the late radiation changes following the treatment of haemangiomata 20-30 years ago, the results of the surgical salvage of tumors recurrent following radiotherapy and the study of acute epithelioma. This diagnosis still has to be made on clinical grounds because of the difficulty and confusion in the histological reports and the clinical course of the tumor (Figure 1). In a review of 160 patients with 173 lesions where the clinical diagnosis was compatible with keratoacanthoma, the histology showed the latter in 73 (53%) patients, well differen-

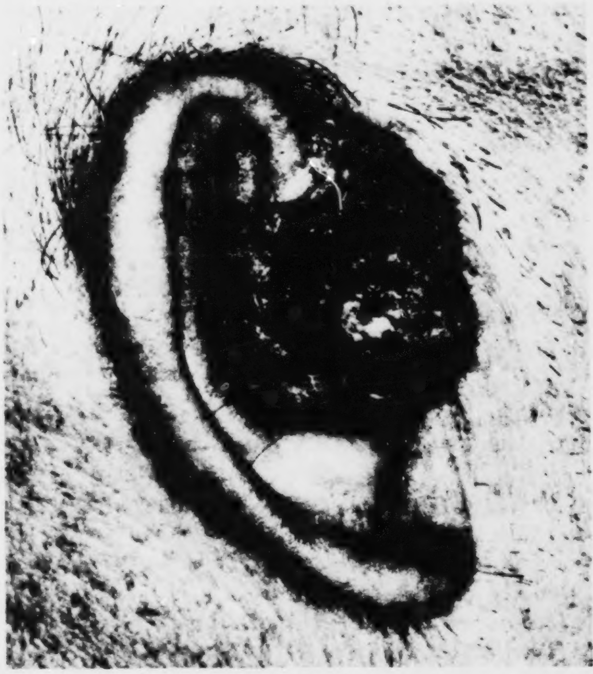

Figure 1. Acute epithelioma. Squamous cell carcinoma or keratoacanthoma?

tiated squamous cell carcinoma in 59 (35%) patients with the others having a variety of diagnoses. The median duration of symptoms was eight (2-89) weeks. Following treatment by surgery or radiotherapy 24/157 (15%) patients recurred and of these 8 (33%) had tumor related deaths.

The clinic attracts tertiary referrals from Ontario and elsewhere. We have the largest dermatologic radiation clinic in North America and are frequently consulted as to the best method of treatment and in particular for the technical details of radiotherapy.

A clinical entity that is becoming more common is that of the Merkel cell tumor or trabecular carcinoma of the skin. In the last three years we have seen approximately 40 patients with this neuroendocrine carcinoma of the skin that was first reported in 1972[1]. It has been likened to small cell carcinoma of the lung and local recurrences, regional lymph node and distant metastases are frequent occurrences.

Actinic damage to the skin with patients having multiple keratoses is an ongoing problem. We do not have the space or resources to establish a sun-damage skin clinic although the need is clearly there.

After 28 years the Picker Zephyr 100 Kv superficial radiation unit was retired and given to the Ontario Veterinary College at Guelph. It has been replaced with a Phillips RT-100 unit which increases our range of treatment options. The electron beam is being increasingly used to treat skin tumors, but because of machine shortages and treatment delays, the majority of patients will continue to be treated with superficial and orthovoltage irradiation.

The follow-up clinics are saturated and so most patients are now discharged after three years to the care of their own doctors.

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Ear Nose And Throat/Head and Neck Oncology

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Approximately 600 new cases of epithelial cancer of the head and neck are seen annually at multidisciplinary clinics held weekly. The majority of patients have disease localised to the primary site or the regional neck nodes and as such are amenable to treatment with curative intent.

■ Prospective Studies

Radiotherapy Versus Radiotherapy And Simultaneous Mitomycin And 5-Flourouracil Infusion For Advanced Carcinomas Of The Larynx And Hypopharynx

This randomized trial has been carried out in collaboration with the Ontario Cancer Treatment and Research Foundation (OCTRF) clinic in Ottawa, the Toronto-Bayview Regional Cancer Centre (an OCTRF clinic) and the Manitoba Cancer Research Foundation Clinic in Winnipeg.

The trial has been supported by the National Cancer Institute of Canada since 1983. Continued support to complete follow-up and analysis of the trial has been provided until 1988. Accrual for the trial was completed in March 1986. A total of 212 patients were entered on study of which 157 were from The Princess Margaret Hospital. A detailed analysis of the study will be carried out in 1987 when adequate time has been allowed for follow-up of all patients entered.

Sequential Chemotherapy And Radiation For Nasopharyngeal Cancer

Between April 1981 and December 1983, 49 of 51 consecutive patients with locoregional carcinoma of the nasopharynx were treated with two courses of chemotherapy given prior to radiation therapy. The results of this single arm prospective study became available in 1985 and are summarized as follows.

Chemotherapy consisted of methotrexate, bleomycin and cisplatin given at three-week intervals, and radiation therapy was scheduled to commence three weeks after the start of the second course. Only one patient progressed on chemotherapy, and of 36 patients with measurable neck nodes, eight had complete and 19 had partial clearance (>50% decrease in cross-sectional area) of these nodes when assessed prior to initiation of radiotherapy.

Despite the high rate of tumor response (75%; 95% confidence limits 59-91%) the actuarial survival and disease-free survival curves were almost identical to those recorded for a consecutive group of 140 historical controls of similar stage distribution treated with radiation alone (see Figure 1 and Figure 2). This chemotherapy provided a high rate of tumor remission but failed to offer long-term benefit to patients when used prior to radiation therapy.

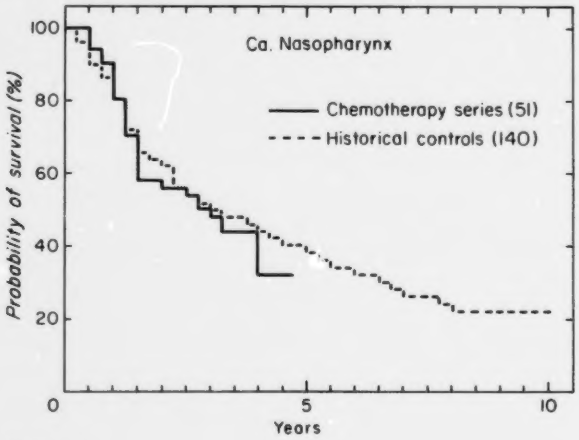

Figure 1.

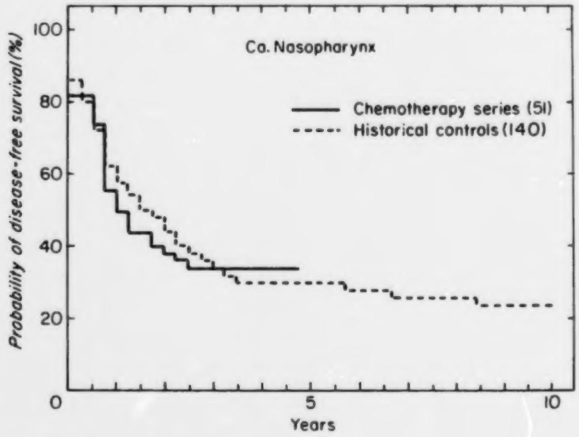

Figure 2.

Elective Lower Neck Node Radiation For Cancer Of The Oral Cavity And Oropharynx (without clinical evidence of nodal metastases)

This trial commenced in 1984 and continues to accrue patients. When completed it is hoped that the optimal treatment volume will be determined for regional lymph nodes which are clinically uninvolved.

Salivary Gland Tumors

Further retrospective analyses have been performed on our experience with 403 patients seen between 1958 and 1980. The first reports were an overall view of these tumors and currently we are making and in-depth review of 271 malignant parotid tumors aimed at assessing prognostic factors and optimum treatment. The most common symptom is a painless lump in the neck. The proportion of advanced (T3, T4) to early (T1, T2) tumors was 1.7:1 and at diagnosis 42 (15%) patients had regional metastases. An analysis for prognostic factors showed that the histology, tumor stage, the presence of regional metastases, age and damage to the facial nerve all influenced cause-specific survival rates. After multivariant analysis the tumor size and the presence of regional metastases were found to be the two most significant factors ($p = < 0.0001$ and 0.004). The well differentiated mucoepidermoid and acinic cell carcinomas had the best prognosis and the undifferentiated and epidermoid carcinomas the worst (Figure 3). We recommended that optimal treatment is the complete excision of the tumor whenever possible and that if there is any doubt about the completeness of surgery then postoperative radiotherapy is recommended. The results of combined treatment in terms of both relapse-free survival and the local relapse-free rate show a great advantage when compared to surgery or radiation alone (Figures 4,5).

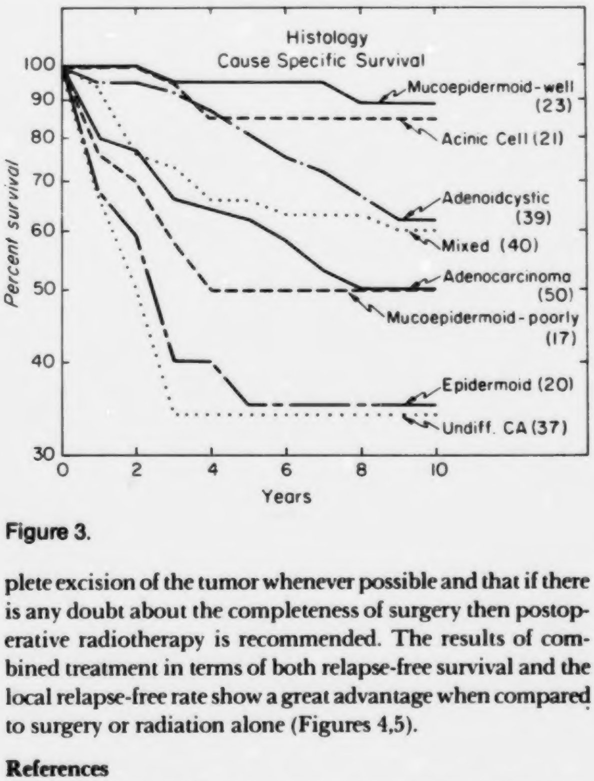

Figure 3.

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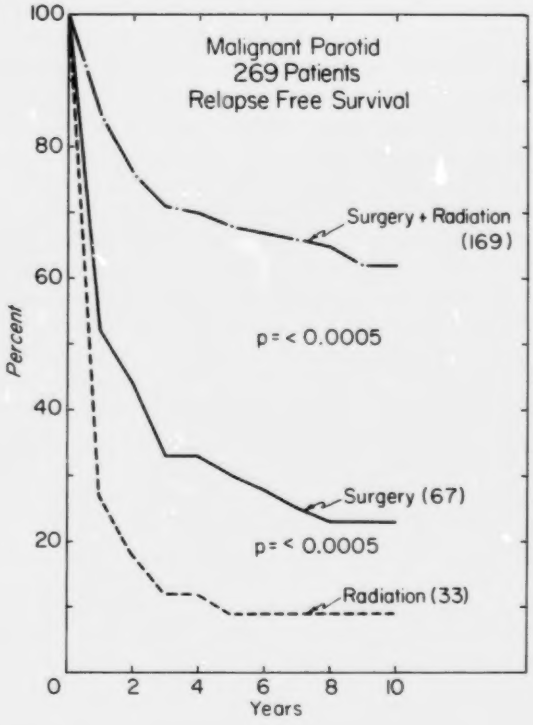

Figure 4.

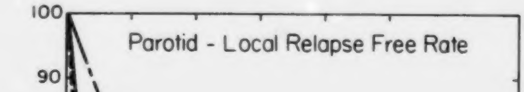

Figure 5.

Lung Cancer

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More than 1,000 patients with carcinomas arising from the lung are referred to The Princess Margaret Hospital each year. Some of these are referred here for radiation only or occasionally for chemotherapy only. As many as possible are put on clinical trials. There is an active multidisciplinary group dealing with lung cancer at The Princess Margaret Hospital. This group interacts with many physicians from other teaching hospitals in Toronto for the purpose of carrying out lung cancer studies.

■ *Small Cell Lung Cancer Studies*

NCI(C) Study

a) BR.4: This study compares six courses of CAV to this combination alternating with VP-16 and cisplatin in patients with extensive small cell lung cancer. The study was stopped about one year ago. Present data suggests that there is a significant response benefit and survival benefit to the alternating arm. Unfortunately, the survival benefit is under two months at the median. Preliminary data from a cost benefit analysis suggest that the gain is sufficiently important for the patient, both financially and in "quality of life", that the small gain should be considered sufficient to change standard therapy for this disease. Further confirmation is necessary from other similar trials ongoing elsewhere. The results of this trial may suggest that the Goldie-Coldman hypothesis is correct. Another possible explanation is that the VP-16 + cisplatin is the better treatment and that the alternating approach is not what has improved the outcome.

b) BR.6: This trial has been ongoing for over a year and has in excess of 100 patients with limited small cell lung cancer entered. Patients receive alternating CAV and VP-16 + cisplatin for a total of six courses. Thoracic irradiation is either given early (during the second course of chemotherapy) with VP-16 + cisplatin or at the end of therapy with the same combination. Prophylactic cranial irradiation is used in this study in patients who are responding and it is given at the end of therapy. It is hoped that giving early thoracic irradiation might improve the results of an alternating regimen in this disease. The study is continuing to accrue patients but early toxicity data suggests that it is tolerable and that a reasonable answer should be forthcoming.

c) An NCI(C) Phase II trial is underway using a combination of VP-16 and the recently marketed platinum derivative carboplatin, in patients with extensive small cell lung cancer with measurable disease. This is a preliminary study to see if a randomized trial will be indicated in the future. Preliminary data from the Marsden (Smith et al) using this regimen is encouraging.

Lung Cancer Study Group (LCSG) Trials

The Lung Cancer Study Group (an international cooperative group funded by the NCI(U.S.) is continuing its small cell study (#832). Physicians at The Princess Margaret Hospital as well as surgeons and medical oncologists at other Toronto teaching hospitals are entering patients on this study. Patients with limited disease receive five courses of CAV and if clinically resectable, are randomized to surgery or not. They all receive prophylactic cranial irradiation and thoracic irradiation, but no further chemotherapy. The value of surgery as an addition to chemotherapy and radiation is being tested in this trial. The EORTC and ECOG are also entering patients on this trial.

Princess Margaret Hospital Local Study

In excess of 600 patients with proven small cell lung cancer who had been on previously completed trials were the subjects of a retrospective analysis to look at prognostic factors in patients with small cell lung cancer. From this analysis we determined that, as with most other studies, stage of disease (limited versus extensive) and performance status are among the most important factors. In addition, we found the markers CEA and LDH to be independently prognostic and that there appears to be some interaction of the two in determining prognosis. LDH seems to correlate quite well with bone marrow involvement, suggesting that if the LDH is normal an invasive procedure can probably be avoided. We also observed that mediastinal status (involved or not) seems to play a major role. The use of new statistical methodologies such as recursive partitioning may help us in the future to devise methods to determine an individual patient's prognostic index.

■ *Non-Small Cell Studies*

Current Lung Cancer Study Group Trials

a) Protocol #801: This study deals with totally resected patients with T_1N_1 and T_2N_0 Stage I non-small cell lung cancer. These patients are randomized to receive four courses of CAP or no additional treatment. The study is closed to accrual and in the follow-up phase. To date no statistically significant differences have been observed between the two arms.

b) Protocol #841: This dealt with patients with resectable non-small cell lung cancer involving the chest wall. Patients were randomized to receive radiation or no additional treatment. Although the question was felt to be important the trial was terminated because of the low accrual over the two year period it was open.

New Lung Cancer Study Group Trials

a) Protocol #851: This is essentially a registry of mesothelioma patients seen throughout the Lung Cancer Study Group. In particular the group is interested in pilot data on the use of pleural pneumonectomy in this disease.

b) Protocol #852: This study is a replacement for the previous protocol #831. It is a pilot study dealing with patients who have non-small cell lung cancer that is technically unresectable but is limited to the chest. Patients receive a new chemotherapy regimen, 5FU and cisplatin concurrent with split-course radiotherapy in the hope of reducing the tumor burden sufficiently to make them resectable. This trial has only recently begun and no data is yet available.

c) Protocol #853: This protocol replaces the previous protocols #772 and #773 and includes all patients with totally resected Stage II and III non-small cell carcinoma of the lung. After appropriate stratification, patients are randomized to receive CAP given for four courses at three-week intervals following their complete resection, or to receive no immediate treatment but be offered either thoracic radiation or chemotherapy at a later time if they relapse. Accrual is ongoing but only a small number of patients have been entered to date.

d) Protocol #85Q: This is a recently activated protocol that includes "quality of life" data for all other active protocols. The methodology used is that developed by Schipper et al in Winnipeg and is also being used by the NCI of Canada and ECOG groups to name but a few.

e) Protocol #861: This is a pilot study to test the value of intrapleural cisplatin + high dose cytarabine in well established pleural effusions to see if this is of value. If this approach turns out to be useful, it may also be tried in patients with mesothelioma.

f) Protocol #862: This is a retrospective pathology trial in which special staining will be done on as many as possible of the previously obtained specimens available at the pathology reference center in Houston. This will hopefully give us additional, up to-date data on the prognostic aspects of special stains.

Further studies are being planned using monoclonal antibodies for diagnostic imaging, laser therapy for obstructing lesions in non-small cell lung cancer, and pilot studies with new biological response modifiers. Many of these should be activated by the end of 1986.

NCI Of Canada Studies

a) BR.5: This study is a three arm trial comparing CAP to vindesine plus cisplatin versus best supportive care in patients with extensive non-small cell lung cancer. Accrual is complete and data analysis is presently underway. The results of this trial are anxiously awaited for the better planning of future trials in this disease.

Other Non-Small Cell Lung Cancer Studies

a) Phase II trial with escalating doses of epirubicin: This study is looking at high-dose epirubicin in previously untreated patients with extensive non-small cell lung cancer with measurable disease. These patients will be looked at initially in a phase I approach trying to determine the safest high-dose that can be used in this population. Then of course, activity will be looked for in the phase II portion of the trial. Doses in excess of 120 mg/m^2 seem to be well tolerated.

b) A phase II trial of 5FU and leukovorin in patients with adenocarcinoma of the lung: Previously untreated patients with adenocarcinoma of the lung with measurable disease will be eligible for this trial. It has been found that 5FU plus leukovorin combined seem to be better than 5FU alone in advanced colorectal carcinoma. It is hoped this same approach will be useful in adenocarcinoma of the lung. This trial will be initiated as soon as the previously described epirubicin trial is complete.

c) Polyamines in lung cancer: This study funded through the NCI of Canada is being supervised by Dr. W.K. Evans formerly of Toronto General Hospital and now in Ottawa. Bloodwork and urine is being collected for varius nutritional parameters including polyamines. It is hoped that a better understanding of metabolism in this disease will be achieved by studying patients prior to treatment, during response and when progression occurs. This may give us a better idea of how we might use new agents such as polyamine synthesis inhibitors as therapy in this disease in future years.

d) The value of magnetic resonance imaging (MRI) in potentially resectable non-small cell lung cancer: This study was carried out through the cooperation of surgeons at a number of teaching hospitals in Toronto. It compared the value of x-rays with tomography and with CT and MRI of the thorax in patients who underwent mediastinoscopy plus or minus thoracotomy. This study had accrued in excess of 100 evaluable patients. Initial analysis of this data suggests that CT scanning and MRI give similar results with no clear cut benefit for the new modality in assessing the mediastinum in these patients.

e) Squamous cell antigen: We are involved in a cross-country trial looking at squamous cell antigen produced by Quadralogic Incorporated. We are screening patients with various types of lung cancer, other malignancies and benign lung diseases as well as healthy patients who are smokers and non-smokers. We hope to find out if this will be a useful diagnostic test as well as possibly having some prognostic implication. No data is yet available.

References

Numerous papers have been published on these studies. Please contact the clinicians for additional information.

Ocular Oncology

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L. Linsmore, R.N., Ophthalmic Assistant
Allan Connor, Photographer

Although there has been an eye clinic since the PMH opened in 1958 the early clinics were mainly devoted to dealing with ocular problems encountered by cancer patients in general and to dealing with the complications following the radiotherapy for head and neck tumors. We have now developed into a multidisciplinary clinic and as an ocular oncology centre it serves Toronto for primary care and the province as a tertiary referral centre. Weekly conferences are held when all new and problem patients are reviewed in a multidisciplinary setting. This provides an excellent teaching format for residents in both radiation oncology and ophthalmology. Last year there were 1839 patient contacts in the clinic.

Pterygium is a degenerative condition of the conjunctiva whereby a fleshy mass spreads across the cornea producing a cosmetic blemish and interferes with vision. It is one of the few benign conditions still treated by radiotherapy. Postoperative strontium electron irradiation in two weekly doses of 1000 cGy has been the standard treatment for years. However, we have not been able to assess our results because of the variability of presentation, multiple previous treatments and different operations. Accordingly, two years ago a prospective randomised study with informed consent was mounted when following surgery, strontium radiotherapy was given with doses of 100 or 1000 cGy. Patient accrual is satisfactory and it is hoped that meaningful results on the value of this treatment will be available within the next few years.

Tumors of the eyelids are one of the most common clinical problems. The majority are treated by radiotherapy with shields being used to prevent damage to the eye. The five-year control rate for basal cell and squamous cell carcinomas are 95% and 93.3% which compares favorably with the results of treatment from other centres.[1] The overall complication rate was 9.6% with fewer than one half rated as serious, and these problems occurred mainly in large tumors that had destroyed human tissues.

An increasing number of lymphoreticular tumors of the orbit are being seen. However, only 42 patients were identified from over 2000 patients with tumors of lymphoid tissue seen between 1958 and 1979.[2] There are two main clinical presentations, those presenting with anterior disease involving the conjunctiva or eyelids and those of the lachrymal gland or orbit. About one-half are primary malignant lymphomas with the first sign of disease being related to the eye or orbit whereas the rest reflect generalised disease in patients that have already been diagnosed and treated. Radiotherapy with doses of 2500-3500 cGy provide effective treatment. For the primary malignant lymphomas the five and ten-year cause specific actuarial survival rates are 70 and 62% and the relapse-free rate 41%.

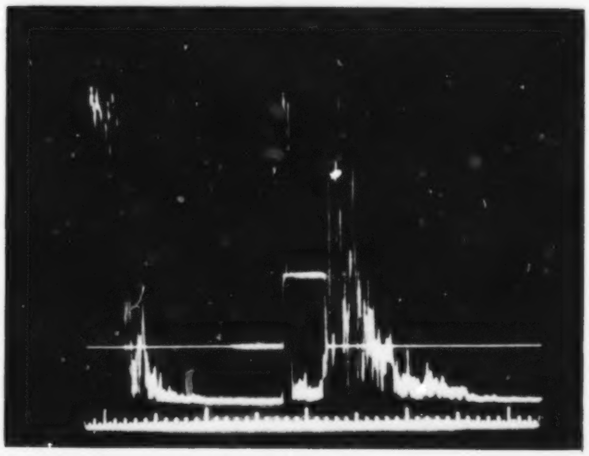

Figure 1. B-scan of a choroidal melanoma.

The biggest increase in the volume of work has concerned choroidal melanomas (Figure 1). Over the last four years we have averaged 39 new patients annually (Table 1). This is a rare condition with an estimated five new cases per million population each year. The standard treatment is enucleation but since 1929 attempts have been made to treat these tumors by radiotherapy. We have been actively involved in irradiating choroidal melanomas since 1971 and have now accumulated over 200 patients. The object of radiotherapy is to destroy the tumor but at the same time to preserve vision. Our earlier five year survival rates were in the region of 50% but have now increased to 84%. This is in part due to earlier diagnosis and the referral of patients at the time of their first symptom. Tumors are divided into small, medium and large. The small ones have an excellent prognosis with survival in the region of 90% at five years whereas only 50% of the large ones survive the period. It is not clear whether enucleation or treatment by radiotherapy is most effective in terms of survival and accordingly a prospective randomised trial with informed consent is being commenced this fall. The Collaborative Ocular Melanoma Study (COMS) is sponsored by the National Eye Institute and the National Institute of Health in Washington and has been generously funded for the next five years. Thirty university centres across North America are participating and valuable information on the natural history of choroidal melanoma and the results of different forms of treatment will be available in the next five to ten years. Most small tumors will be observed and so growth rates can be calculated and treatment initiated if and when growth is documented. Patients with medium tumors will be randomised into treatment by enucleation or by the application of a radioactive I-125 plaque to deliver a dose of 10,000 cGy to the apex of the tumor. Those with large tumors will be enucleated with or without 2000 cGy preoperative radiotherapy. Our clinic has a large history in the development of radioactive plaques starting with tantalum wire and gold grains in the 1970s and then using iridium wire and now iodine seeds. An external 60 Cobalt irradiation D-beam technique was also developed for treating small tumors at the back of the eye.

Choroidal melanomas can not be biopsied, and so assessments by meticulous direct or indirect ophthalmoscopy are supported by serial fundus photography and ultrasound profiles (Figure 2).

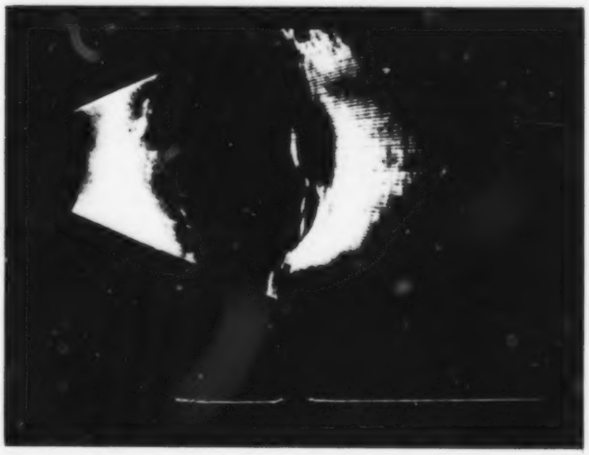

Figure 2. A-scan showing a profile through the eye. The irregular internal reflectivity is due to the varied internal histologic structures.

New research is being initiated using photoradiation and hematoporphorin. This substance can be concentrated in tumors and when exposed to a laser beam absorbs energy and the tumor may be destroyed.

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Management Of Pain In Cancer Patients

R.J. Evans, M.D., Consultant, Director of Toronto General Hospital Pain Clinic
C.P. Watson, M.D., Consultant Neurologist
C. Bubela, M.D., Consultant Anaesthesiologist

Goals Of The Pain Clinic

Patient Care—To provide a plan of treatment, rehabilitation and satisfactory quality of life.

Clinical Research — Pharmacological/epidemiological and therapeutic innovations.

Education — For under and postgraduate medical students and allied health care personnel.

Approximately 100-150 patients are referred to the Pain Clinic at The Princess Margaret Hospital per year, with the prime complaint of unrelieved pain in spite of treatment. This represents approximately 20% of the new patient referrals to the entire Pain Service based at Toronto General Hospital.

The etiology of pain, is related to advancing malignant disease in 95% of patients. Sixty percent of patients have pain related to local recurrent disease, 35% have pain related to metastatic disease and the remaining 5% have pain which is totally unrelated to the malignant process.

Approximately one-third of patients come from the province outside of Metro Toronto. Decision regarding investigations and definitive treatment are made by an informal interdisciplinary team, consisting of oncologist, radiotherapist, family practitioner and in the case of definitive procedures, with the neurosurgeon, orthopaedist or rehabilitation medicine departments. Interdisciplinary co-operation between team members has been the mainstay of the clinic, and detailed follow-up procedures have provided the information necessary to learn, develop innovations and teach so that experience gained can benefit others.

In the past year, topics such as "Pain in children under 18 years", "Postherapeutic neuralgia", "Pain associated with head and neck tumors", "Use of Epidural reservoirs for administration of morphine", "Chylothorax following neurolytic nerve blocks for cancer", "Pain Syndromes related to rectal carcinoma", and "Pain associated with advanced carcinoma of the lung" are some of the topics which have been studied and results published.

The Pain Clinic at The Princess Margaret Hospital has been visited by many from other countries, as well as North America, and this has enhanced awareness of difficulties being faced in controlling intractable pain related to cancer.

In Toronto, an inter-hospital, interdisciplinary, collaborative group known as UTOPIA (University of Toronto, Ontario, Pain Institute Associates), has been recommended. The prime purpose of such a group would be improved communication, education, collaborative research and improved patient care. Specific proposals have been made by an enthusiastic group of dedicated workers in pain research, to the Associate Dean of Clinical Institutional Affairs, and it is hoped that the impact of collaboration of basic scientists, pharmacologists and clinical care personnel, will further improve pain treatment for everyone.

Diagnostic Imaging Department

D.F. Rideout, M.B., Chief, Department of Diagnostic Imaging
R. Blend, M.B., Radiologist
S. Herman, M.D., Radiologist
I.F. Majesky, M.D. Radiologist
P.Y.C. Poon, M.B., Radiologist

The Department of Diagnostic Imaging provides services in conventional radiology, computed tomography, ultrasound, xeroradiography, and magnetic resonance imaging.

The total volume of conventional radiology has increased 4% over last year to 37,133 examinations while the volume of special procedures such as lymphography, venography and myelography is stable. The increase in conventional radiology is distributed over a very wide range of examinations.

The demand for ultrasound service has risen 12% over the past year to a total of 1,120 examinations, and the demand for computed tomography has increased by 7% to a total of 6,817 examinations.

The volume of thermography has not changed significantly and for mammography there were 2,304 examinations.

In magnetic resonance imaging 435 examinations were performed during the first three months of 1986 which is in keeping with the volume predicted for this modality.

The workload for the year for all of these imaging modalities combined adds up to 1,850,835 standard work units for the year.

■ Clinical Research Activities In The Department of Diagnostic Imaging

Ultrasound

A breast imaging group led by Dr. N.F. Boyd has established that mammographic dysplasia is strongly associated with breast cancer particularly in women aged less that 50. A study is now being conducted to determine whether this high risk pattern which has been detected using mammography can also be detected reliably using ultrasound. The benefit of using ultrasound for this detection would come from avoiding ionizing radiation with its attendant risks. The investigators involved in this study at OCI are Drs. Boyd, Kaiser, Blend and Rideout.

Comparative Studies In High Technology

Many of the staff have been involved with staff from other OCI/PMH departments in studies to evaluate the effectiveness of different modalities for various diagnostic and assessment purposes. The results of these studies have been published and/or presented at numerous international conferences during the past year.

A comparison of MRI and CT in the detection of mediastinal involvement in brochogenic carcinoma found that the two modalities were equally effective in the detection of neoplastic involvement of mediastinal lymph nodes. Drs. Poon and Rideout were involved in this study which has been accepted by Radiology for publication.[1]

Drs. Majesky, Poon and Rideout were also involved in a comparison of MRI and CT in the detection of brain metastases. In examinations done within 10 days of each other, it was noted that MRI is more sensitive to the detection of small areas of edema, gliosis or demyelination than CT. By using positive contrast enhancement, CT was shown to be more sensitive in delineating the extent of the actual tumor and in demonstrating response to treatment and reduction in tumor size.

A comparison of MRI, CT and radionuclide scintigraphy in the detection of liver metastases involved Dr. Poon from this department and was presented at the 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, 1985.

An overview of the impact of all of these technologies was published by Dr. Blend in the Annals of Royal College of Physicians and Surgeons.[2]

Computed Tomography

Drs. Rideout, Herman and Majesky were involved in a study of inter and intra-observer reliability for computed tomography in advanced ovarian cancer. This study showed that CT is not a reliable modality in the detection of tumor masses in the pelvis and abdomen from ovarian cancer.[3]

Drs. Poon, Majesky and Rideout also participated in an assessment of acute radiation induced pulmonary findings using computed tomography.[4]

Magnetic Resonance Imaging

Members of the Diagnostic Imaging Department have been involved in several studies of MRI which have been presented and/or published during the past year: Dr. S. Herman in a study of magnetic resonance imaging of soft tissue tumors of the extremities; Dr. Poon in studies of MRI in clinical radiation oncology[5]; Dr. Herman in a study of MRI of the hips and surrounding tissues; Dr. Poon in a study of MRI in iron overload in liver tissues[6]; and Drs. Blend and Poon in a study of MRI in spinal cord compression.

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Clinical Laboratory Services

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L.M. Sugar, M.D., Pathologist
T. Treger, M.D., Pathologist

The clinical laboratories at OCI/PMH consist of the Department of Pathology and the Department of Microbiology. The Department of Pathology, which is a shared service with Wellesley Hospital, consists of the division of Anatomic Pathology (which includes Cytology and Electron Microscopy), Clinical Biochemistry, Hematology, Blood Bank and the I.V. Nurse Service. The latter is an acute care general hospital located immediately adjacent to OCI/PMH. During the year, 12,203 surgical pathology cases were processed, an increase of 2.5% over the previous year. The number of autopsies from the two hospitals remained relatively constant at 186, as did reviews of outside pathological material on patients referred to The Princess Margaret Hospital (3,128 cases).

The Cytology Laboratory dealt with 9,836 specimens. This number included 2,561 non-gynecological and 603 fine needle aspiration biopsy specimens. The caseload in the laboratory increased by 15.7% in 1985-86. This resulted almost entirely from the increased activity of the Colposcopy Unit at the Wellesley Hospital. This is part of the Gynecological Oncology Program recently established at this hospital. The continuing expansion of this program will affect both Surgical Pathology and Cytology caseloads accordingly during the coming years. In Electron Microscopy, 271 cases were processed, and a new Zeiss EM902 electron microscope, an instrument developed in the OCI/PMH research labs, was installed in the department.

The division of Clinical Biochemistry performed 364,639 tests during 1985-86. Tests done on out-patients represented 44.2% of this total workload, up from 42.6% in 1984-85. In 1985-86 there was a 4.3% increase in the number of tests done on out-patients, and a 2.6% decrease in those done on in-patients. It is interesting to note that about 10% of the 1984-85 workload consisted of BUN's. By dropping this as a routine test, we have managed to keep the total workload approximately the same in 1985-86.

In the division of Hematology, a total of 542,638 tests were done in 1985-86. This represented an 8.1% increase over the previous year's total on out-patients. The Hematology Laboratory has been computerized since April 1, 1985. The results of all hematology tests are now available in doctors' offices, nursing units and clinics which have terminals, as soon as the specimens have been processed through the laboratory's automated instruments.

The total number of blood components issued for transfusion by the Blood Bank went up from 15,042 (from April 1984 to March 1985) to 18,959 (from April 1985 to March 1986), an increase of 26%. There has been a greater demand for single donor platelets from platelet transfusion therapy compared to previous years. Single donor platelets are available through special arrangement with either The Princess Margaret Hospital Cell Separator or the Canadian Red Cross Pheresis Laboratory.

Psychological Medicine

Clinical Program

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M.J. Deachman, R.N., Psychological Medicine
D. Ramsay, M.D., Psychiatrist, Psychological Medicine
A. Zielinsky, M.D., Psychiatrist, Psychological Medicine

Description of Services

Psychological Medicine is a multidisciplinary team which interacts with other hospital services and community resources for cancer patients. As well. subspecialized resources such as vocational rehabilitation counselling are mobilized where needed.

Patients and significant others experiencing psychological distress are given a comprehensive assessment to determine and prioritize their areas of greatest need. A diagnosis is made where appropriate and recommended solutions to difficulties are specified both to the patient and the attending physician. Where follow-up is to be done by Psychological Medicine, the patient or significant others will be seen until a mutually satisfactory outcome is reached.

Pre-assessment contact with the patient may be arranged for those patients who are sensitive to referral and may need some further information and reassurance about the process. As well, some assistance may be given to staff where the indications for referral are not clear cut.

Treatment

Specific psychological treatments are given where indicated, including psychotherapy, some forms of relaxation training, marital therapy, supportive psychotherapy and bereavement work.

Pharmacological treatments are prescribed for some conditions such as major depressions, overwhelming anxiety and organic mental conditions. Specific psychiatric conditions such as the major psychoses are treated as in other settings.

General support and mobilization of resources are provided for all patients or significant others assessed or followed by Psychological Medicine.

Research Program

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D. Tritchler, Ph.D.,
J. Till, Ph.D.,
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D. Ramsay, M.D., Psychiatrist, Psychological Medicine
B. Johnstone, Ph.D., Postdoctoral Fellow, Biology Division
J. Sturgeon, M.D., Medical Oncologist
S. Sutcliffe, M.D., Medical Oncologist

Choosing A Risky Treatment — Psychosocial Aspects of Risky Choice (Silberfeld, Phoenix, Lockwood Tritchler, Till)

Seventy volunteers were presented with a hypothetical decision to accept or reject a risky treatment for themselves and/or others. The risky treatment was bone marrow transplantation. Volunteers were shown a videotape movie for patients who had already accepted bone marrow transplantation. After seeing the videotape, volunteers were asked to accept or reject bone marrow transplantation for themselves and for another if they were a patient faced with that choice. As well, they filled out three psychological instruments. The Rokeach Value Survey, the Depressive Attributional Style Questionnaire and the Rosenberg Self Esteem Scale. The results suggested that those accepting the risky treatment had a different value structure and a different attributional style than those who chose to reject the treatment. Self-esteem did not appear to come into the decision-making.

(Under review, American Journal of Psychiatry)

Psychosexual Morbidity Related To The Genital Origin Of Cancer (Johnstone, Phoenix, Sturgeon, Till, Sutcliffe)

The genital origin of cancer along with the role of orchectomy as a determinant of subsequent psychological and sexual morbidity has been examined in this study by detailed analysis of psychological, sexual and physiological attributes in patients with cancer of the testes in comparison to patients with Hodgkin's disease. The two patient groups experienced similar investigations, therapy, favorable prognosis and are comparable in similarity of their epidemiological characteristics. On the basis of the data presented, patients with testes cancer exhibited levels of psychiatric symptomatology following diagnosis that are qualitatively similar to those patients with cancers at other anatomic sites. But following therapy, patients with testes cancer failed to resolve their psychiatric distress and manifested a worsening in sexual relationships. The data was consistent with the hypothesis that testes cancer and orchectomy result in psychiatric and sexual morbidity that persists following otherwise successful therapy.

The Development of Psychological Medicine Services In An Oncology Hospital (Ramsay, Deachman, Silberfeld)

This paper reviews the historical development of the Psychological Medicine service at The Princess Margaret Hospital over the past six years, and describes the profile of work and patients seen by statistical analysis. A review of the literature covers incidence reporting on psychiatric morbidity, treatment effectiveness and the few papers describing various developments in the organization of psychological services to the cancer population. The service at The Princess Margaret Hospital is described along its historical development. A statistical analysis outlines the patient population in terms of DSMIII diagnoses and compares this with the PSYCOG study results. The frequency and distribution of patient health concerns using Weissman's table of health concerns is described and a survival curve comparing psychological medicine referrals with non-referrals is presented. A statistical profile of referral patterns, assessments and follow-up visits by the psychiatrists and the psycho-social liaison nurse enables the reader to appreciate the extent and kind of work done. This is followed by a discussion of the findings and the implications for the further development of the service. (Under review, Canadian Journal of Psychiatry)

The Use Of Progressive Relaxation With Oncology Patients (Deachman, Silberfeld)

The impact of using relaxation techniques to reduce stress levels was assessed using a group of twenty-five oncology inpatients. The technique, involving physical and mental relaxation, was taught as a self-help skill through the use of instruction, practice and feedback regarding progress. The results, assessed by the patients, the staff nurses and the relaxation therapist (Deachman) suggested that patients in general responded positively to using the relaxation tapes. The level of compliance may have been due in part to the patient's response to the desire of others to help. It appeared that the additional personal interest was of greater effect than the relaxation itself. But it was believed that the progressive relaxation technique used did have some helpful benefit although it possibly required better training and more practice.

Sex-Role Stereotyping In The Clinical Judgement Of States (Deachman, Silberfeld)

This study examined the manner in which forty-five male and forty-five female nurses prioritized the importance of patient concerns and how each group described a mature, healthy, socially-competent adult woman. Sex-role stereotyping was assessed through the use of a stereotype questionnaire designed by Broverman et al. The areas of predominant concern for patients were assessed through use of a ranking of seven major concerns taken from the work of Project Omega. The data was consistent with the hypothesis that only minimal differences were found between the manner in which male and female nurses prioritized patient concerns. This appeared to coincide with complete agreement or sex-role stereotyping. The only difference was in the valuing of friendships which was ranked differently for the male and female nurses and was therefore left open to speculation and requires independent confirmation. It was believed that sex-role stereotyping in the perception of health state was worthwhile looking into to prevent bias from leading to the provision of unequal care. (Under review, Canadian Journal of Psychiatry)

Other Clinical Research Projects

Antibiotic Studies

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Physicians at The Princess Margaret Hospital have been involved in multi-centre national trials on new antimicrobial agents as they become available for clinical evaluation.

IC.4

This trial funded through the NCI of Canada and Squibb Pharmaceuticals of the U.S. and Canada has been completed. It compared azthreonam plus cloxacillin versus tobramycin plus azthreonam versus tobramycin plus moxalactam. The tobramycin plus moxalactam was found to be superior to the other two arms as far as efficacy. In general, toxicity was not remarkably different but there appeared to be a strong trend in favor of an increased frequency of fungal superinfections in the tobramycin/moxalactam arm. This suggests that "colonization resistance" may protect patients against superinfections and that one must be cautious about using only response rates for efficacy evaluation in studies where superinfections turn out to be serious complications of therapy and may possibly be fatal.

IC.6

This study is a cooperative trial between the NCI of Canada and the EORTC in Europe. Febrile neutropenic patients including bone marrow transplants are randomized to one of two arms. All patients receive amikacin plus ceftazidime and patients are randomized to receive or not to receive vancomycin in addition. With the high frequency of gram-positive infections noted in some of our previous trials and those in other parts of the world, this may prove to be a very important question. This also represents a new cooperative effort between Canadian and European investigators.

Ceftriaxone Versus Cefotaxime

We are continuing to enter patients on a double-blind randomized trial comparing a single dose of a long-acting third generation cephalosporin, ceftriaxone to four doses of a standard shorter half-life third generation cephalosporin, cefotaxime. If the study drug turns out to have at least equivalent activity, an agent that can be given once a day, possibly on an out-patient basis will be available to the physician for serious infections. Preliminary analysis appearing in abstract form with over half the patients entered suggests no obvious difference between the two treatment arms.

Vancomycin Versus Teicoplanin

We hope to begin a trial comparing vancomycin and teicoplanin using a double-blind design in the treatment of gram-positive line infections. Teicoplanin is a new vancomycin derivative with a very long half-life (>30 hours) which can be given once a day and appears to be more active and perhaps lesstoxic than the presently available vancomycin. This trial will be run across the country and with the increase in the use of central lines in patients with malignancy. The results of this trial may prove to be very important to the practice of oncology.

Oxyquinolone

We will soon begin to enter patients on a randomized trial comparing the oxyquinolone (enoxacin) given initially parenterally followed by oral therapy to a more standard regimen of an aminoglycoside and ampicillin. This will be used in patients with urinary tract infections requiring parenteral therapy (primarily pyelonephritis).

Orthopedic Pathology Research

V.L. Fornasier, M.D., Pathologist

Orthopedic Pathology is a major component of the combined Princess Margaret Hospital and Wellesley Hospital Department of Anatomical Pathology. Within this department, a number of diverse research activities have been undertaken.

A major oncological activity includes participation in the Canadian Sarcoma Task Force, in the Bone Tumor Panel of the Canadian Tumor Reference Centre, in the weekly University of Toronto Sarcoma Rounds, and the weekly Sarcoma Tumor Board. This provides a wide base of experience and review material for the departmental orthopedic registry.

Bioreaction To Prosthesis And Prosthetic Materials

The study of bioreaction to prosthesis and prosthetic materials is a major area of study. The assessment of biological and biomechanical acceptability of iso-elastic prosthesis has been undertaken with the support of the Geriatric Society of Canada. An animal study for the assessment of Weill ring and Muller stem components of hip arthroplasties has been undertaken in dogs under the support of the Muller Foundation. Under these projects, prostheses are being implanted in animals in conjunction with the small animal clinic of the University of Guelph and upon harvesting, will be assessed radiographically and histologically for tissue reaction and acceptability.

Under the auspices of Stanford University and the Orthopedic Academy (OREF), a variety of plastic and metal biomaterials is being implanted into animals bones to test the cellular degree and type of reaction . It has long been known that failure of articular prosthesis is associated with the formation of a membrane characterized by macrophages that contain phagocytosed particulate debris. This study will attempt to define the type of cellular reaction and the extent of the cellular reaction to various types and sizes of particulate debris from biomaterials used in implantation arthroplasties.

Metabolic Bone Disease

Metabolic bone disease continues to provide a variety of research interests. Studies are ongoing on the effect of fluoride on bone accretion rates, with the support of the Canadian Geriatric Research Society and the Research Institute of St. Joseph's Health Centre. Recently, the finding of aluminum deposition in osteoid in patients on chronic renal dialysis suggested the possibility of a toxic effect of aluminum on bone mineralization. Therefore a study has been initiated as a conjoint effort of the bone and mineral group (a Deconal Group of the University of Toronto). Using the electron energy loss spectroscopic potential of the electron microscope recently developed at The Princess Margaret Hospital by Dr. Peter Ottensmeyer, it is hoped to identify the pattern of development of aluminum deposition and confirm its toxicity and the effect of treatment in controlling, preventing and reversing this aluminum toxicity to bone.

Inflammatory Arthropathy

Because of the close association of OCI/PMH with the Wellesley Hospital and its Rheumatic Disease Unit, a conjoint study has been developed to test the effect of snake-venom-derived phospholipase subcutaneously and intra-articularly in the production of a model for an inflammatory arthropathy. Current studies involve the development of "air pouches" in subcutaneous tissues of rats and mice where the interaction between phospholipase and a variety of inhibitors to the inflammatory process can be studied. We hope to develop a model for testing the ability of anti-inflammatory agents to control the inflammatory aspects of inflammatory arthropathies.

Biomechanical Significance Of Metastases In Femoral And Vertebral Bone

In conjunction with the Orthopedic Department of the Wellesley Hospital, studies have been developed to test the biomechanical significance of metastases in femoral and vertebral bone. Metastatic carcinoma may weaken bones leading to fracture but there is no accurate way of reliably predicting the risk of fracture once a metastasis has been identified. The study will test pre-determined defects in the contour of the femoral shaft, and will determine the failure stresses that cause collapse of vertebral bodies. It is hoped to determine the significance of the stress rising effect of discrete metastases in a long bone that will eventually lead to bone failure (fracture). Once these biomechanical factors are determined, they will be used to predict risk factors for fracture in bones secondary to metastases.

The Influence Of Campylobacter Pyloridis As A Potential Pathogen In Acid-Peptic Disease (Duodenal And Gastric Ulcers, Gastritis, Etc.)

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The potential significance of Campylobacter pyloridis in acid-peptic disease became apparent when it was demonstrated that over one-third of patients with this disease harbour this microorganism in the stomach. The study now in progress compares means of diagnosing C. pyloridis (bacteriological culture versus urease test versus histology), evaluates the degree of gastritis associated with the presence of these potential pathogens, and looks into the effect of antimicrobial therapy on the evolution of the disease.

Preliminary findings indicate an association between the presence of Campylobacter pyloridis and acid-peptic disease, and a positive effect of antimicrobial therapy on its clinical evolution.

The Use of Morphometry To Estimate Prognosis In Breast Cancer

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Recent evidence in the medical literature suggests that quantification of certain cellular parameters in the histological sections of malignant tumors is helpful in improving the accuracy of predicting its prognosis. The size of the tumor cell nucleus is roughly proportional to the number of chromosomes on the one hand, and to the intensity of cellular metabolism on the other hand. Furthermore, the incidence of mitoses is an indicator of the speed at which the tumor proliferates, and the amount of neoplasm found away from the primary tumor mass is an indicator of its potential for invasiveness. These three parameters are quantified and statistically evaluated with relative ease with today's computer-aided measuring technology.

Female breast cancer in particular presents a great interest in this respect, because it is the most common malignancy in women, and because the natural outcome of the disease is quite variable. We are currently completing a retrospective review of 92 cases of stage 1 and 2 breast cancer diagnosed in the Department of Pathology of The Ontario Cancer Institute between 1970 and 1975. The morphometric parameters of these tumors were compared with the outcome of the disease 10 years after the original diagnosis. The conventional clinicopathological variables considered were: age, diameter of primary tumor, number of metastatic axillary lymph nodes, histological type, presence of tumor necrosis and presence of glandular differentiation. Morphometric variables considered were: nature of the primary tumor margin (sharply demarcated versus infiltrative), nuclear area, nuclear perimeter, longest and shortest ellipse diameters and number of mitoses per 10,000 cells.

Results of the study indicate that the accuracy of the prediction of outcome in patients with at most one axillary lymph node metastasis is significantly improved with input of morphometric parameters. Sharpness of the gross tumor margin (indicating lack of invasiveness), and longest diameter of ellipse (a nuclear parameter indicating intensity of tumor cell metabolism) were the best predictorss. For patients with more than one lymph node metastases on the other hand, morphometric parameters do not add to improved accuracy. Further evaluation of the present findings will be pursued in a prospective study.

Biological Research and Physics Divisions

Solid Tumors

The Role Of P-Glycoprotein In Multidrug Resistance

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Multidrug resistance (MDR) describes a complex phenotype whose predominant feature is resistance to a wide range of structurally unrelated cytotoxic agents, many of which are anticancer drugs. This phenotype is frequently found in mammalian cell lines selected for resistance to a single drug. Reduced drug accumulation appears to correlate with the resistance expressed. Thus, understanding the basis of the MDR phenotype may provide insights as to how mammalian cells modulate the intracellular levels of diverse compounds. In addition, of particular clinical relevance is the realization that tumor cells acquiring a MDR phenotype may be rendered non-responsive, even to a combination of different drugs.

We have made significant progress in the past three years towards understanding the molecular basis of multidrug resistance. Although a wide variety of biochemical changes have been detected in MDR cell lines, the most consistent change is the increased expression of P-glycoprotein, a plasma membrane glycoprotein of approximately 170,000 daltons. Monoclonal antibodies have been raised against hamster P-glycoprotein and these antibodies detect the presence of this membrane component in different MDR human and animal tumor cell lines. The level of P-glycoprotein expression correlates with the degree of drug resistance. Significant levels of P-glycoprotein have been detected in some biopsies of patients with advanced malignancies.

A number of P-glycoprotein cDNAs have been cloned. Southern blot analyses using the cDNAs as probes indicate that P-glycoprotein is encoded by a family of closely related genes. In many MDR lines, the P-glycoprotein genes are amplified. Gene transfer studies show that P-glycoprotein DNA sequences are transfected and amplified exclusive of flanking genes in multidrug-resistant transfectants. These and other studies indicate that P-glycoprotein is the causative molecule mediating multidrug resistance.

Structural analysis of the cloned P-glycoprotein cDNAs has provided unexpected clues to the function of P-glycoprotein. A striking homology with hemolysin B and to a lesser extent, a group of energy-dependent bacterial transport protein has been observed. Thus, by analogy, one function of P-glycoprotein may be in the energy-dependent export of a wide variety of drugs and compounds. The level of homology between P-glycoprotein, a mammalian protein, and the bacterial proteins is unprecedented. The evolutionary conservation of P-glycoprotein suggests that it plays a very fundamental role in cell biology.

We propose to investigate the functional role of P-glycoprotein in greater detail. Structural analysis of the different P-glycoprotein gene members will continue, along with studies to investigate their differential expression in normal and malignant tissues. Effort will be made to determine to what extent P-glycoprotein DNA sequences can functionally replace bacterial hemolysin B protein DNA sequences. Because of the ease of molecular genetic manipulation in bacteria and the advantage of a rapid bacterial assay for function, success in this effort will provide the foundation on which extensive and sophisticated structure: function studies can be made. In addition, such a system may provide a means for screening compounds that may be useful to overcome clinical drug resistance.

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Studies on Epithelial Growth Control and Carcinogenesis

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Since the great majority of human cancers are carcinomas (i.e. derived from epithelial tissues) there is a compelling need for study of regulation growth and differentiation in epithelial cells. In particular, molecular information is required about the processes involved in stem cell behaviour since these cells are the source of normal tissue renewal and the origin of epithelial tumors. This program utilizes a number of human and rodent epithelial models to study regulation of gene expression and carcinogenesis.

Role of Epidermal Growth Factor Receptor in Human Malignancy

We have been studying the mechanisms whereby abnormalities in the EGF receptor can facilitate the unregulated growth associated with malignancy. We have utilized human breast and squamous carcinoma cell lines to study gene amplification events associated with over-production of the receptor protein and how these events relate to tumor initiation, growth, and progression *in vivo.*

Differentiation of Secretory Breast Epithelium

Human breast carcinoma cell lines can be induced to undergo differentiation-related events under the influence of sodium butyrate. We are studying this process at the level of expression of milk-related proteins and utilizing the cells as sources of differentiation stage-specific mRNA. We hope to be able to identify cDNA clones expressed during differentiation from a library generated from lactating human mammary gland and to utilize these clones to investigate control of gene expression.

Studies of Stem-Cell Gene Expression and Carcinogenesis in Rat Intestinal Mucosa

We are studying gene expression in rat small intestinal stem cells by isolating cDNA clones which have differential expression in fetal intestine, adult intestine and immortalized cell lines generated from rat intestinal stem cells. Probes representing stem cell expressed genes will be useful in studying mechanisms of growth and differentiation control in fetal and adult intestine during development and tissue maintenance respectively.

In addition, we are utilizing the immortalized cell lines as recipient cells in gene transfer experiments to study the role of oncogene and growth factor expression in carcinogenesis of the gastrointestinal tract.

Modelling the Role of Stem Cells in Tumor Growth

We have used tumor cells obtained from malignant ascites of human ovarian carcinoma to test the concept that human carcinoma contain a small proportion of stem cells equivalent to the normal tissue stem cells. By analyzing cell differentiation features and the tissue culture clonogenic growth potential of individual cells we have been able to obtain estimates of the size of the stem cell population and a limited amount of information about its biological behaviour. Based on these data, we have constructed mathematical models which seek to explain the properties of tumors in terms of probability functions for cell renewal or differentiation of the tumor stem cells.

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Metastasis

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Mechanism Of Metastasis

Recent research in several laboratories indicates that tumor cells exhibit different metastatic ability, and has suggested that specific cell phenotype(s) are an important determinant of the probability that a given cell will form a metastasis. Our work with two experimental tumors, the KHT Sarcoma and

	Individual (# of cells injected)		Mixed (# of cells injected)	
	KHT-P*(10^4 cells)	B9 (2×10^4)	KHT-P*(10^4 cells)	B9 (2×10^4 cells)
Rate of generation of variants	1.2×10^{-4}	5.5×10^{-5}	1.1×10^{-4}	5.2×10^{-5}
	①	②	③	④

Spearman Rank Correlation

Col ① vs Col ③ $r_s = 0.99$ sig $p \ll 0.01$
Col ① vs Col ④ $r_s = 0.87$ sig $p < 0.01$
Col ③ vs Col ④ $r_s = -0.04$ NS

Table 1. Results of an analysis of the generation of metastatic variant cells in clones of KHT-P and B9 cells, tested either as individual populations or as a mixed population in $C_3B_6F_1$ hybrid mice. The Spearman rank correlation was done using the values for the individual clones.

the B16 melanoma cell lines F1 and F10, has indicated that during growth, unique phenotypes, which predispose the cells to be able to form metastases, are generated stochastically at a high rate (see Figure 1). In particular, we have demonstrated that B16F10 cells generate metastatic variants at a higher effective rate than B16F1 cells, a finding which may explain why B16F10 cell populations are more highly metastatic than B16F1 cell populations. We have also demonstrated that this phenotype is relatively unstable and can be lost rapidly during growth *in vivo* or *in vitro*; the metastatic variants probably need to express their unique phenotype only during the initial phase of development of a metastasis. The metastatic ability of these cell populations is thus in a state of dynamic equilibrium. We have proposed a model of "dynamic heterogeneity" in which it is postulated that within a tumor cell population a small variant sub-population is expressing a metastatic phenotype at any given time; this sub-population is maintained by generation and loss of metastatic variants. This model explains why it is often found that cells isolated from metastases are not more metastatic than their parent tumor cell populations.

We have proposed that the mechanism involved in the generation of the unstable metastatic variants may be gene amplification. If this hypothesis is correct it might be expected that the highly metastatic B16F10 cell line would demonstrate a greater ability to undergo gene amplification than the less metastatic B16F1 cell line. We have been studying the ability of these cell lines to generate variant cells resistant to the drugs methotrexate (MTX) and N-phosphonacetyl-L-aspartate (PALA), resistance to which usually arises as a result of gene amplification. Our results indicate that variant cells resistant to a given concentration of MTX or PALA are generated more rapidly in B16F10 cell populations than in B16F1 cell populations. This result is consistent with our hypothesis and supports the idea that gene amplification may be involved in the generation of metastatic variants. More direct support for the hypothesis is required however, and we are currently attempting to isolate populations of cells, all of which are expressing a metastatic phenotype, so that more direct studies are possible.

We have also examined whether the heterogeneity in metastatic ability between populations derived from different clones, and the variability which is observed between different mice injected with cells from the same population, can be explained by differences in response to the tumor cells among individual animals. KHT Sarcoma cells and a line of B16F10 melanoma cells were injected intravenously, either separately or as a mixture, into groups of $C_3B_6F_1$ hybrid mice, and the number of metastases formed by each cell type (white and black respectively) was counted. A wide range in the number of metastases formed in individual animals was observed for both cell populations, but there was no correlation between the number of metastases formed by the two cell populations in the same animal. Similar results were obtained when the cells were injected intramuscularly and the number of spontaneous lung metastases was counted. These results indicate that animal to animal differences are unlikely to explain the range of variation observed. Parallel clonal populations derived from the two cell lines were also examined in the same system and Luria-Delbruck fluctuation analysis was performed so that the rate of generation of metastatic variants during the growth of the clonal populations could be calculated. The results are illustrated in Table 1 and indicate that the rate calculations were independent of whether the animals were injected with a mixture of two clonal populations or with individual clones. These results again indicate that any

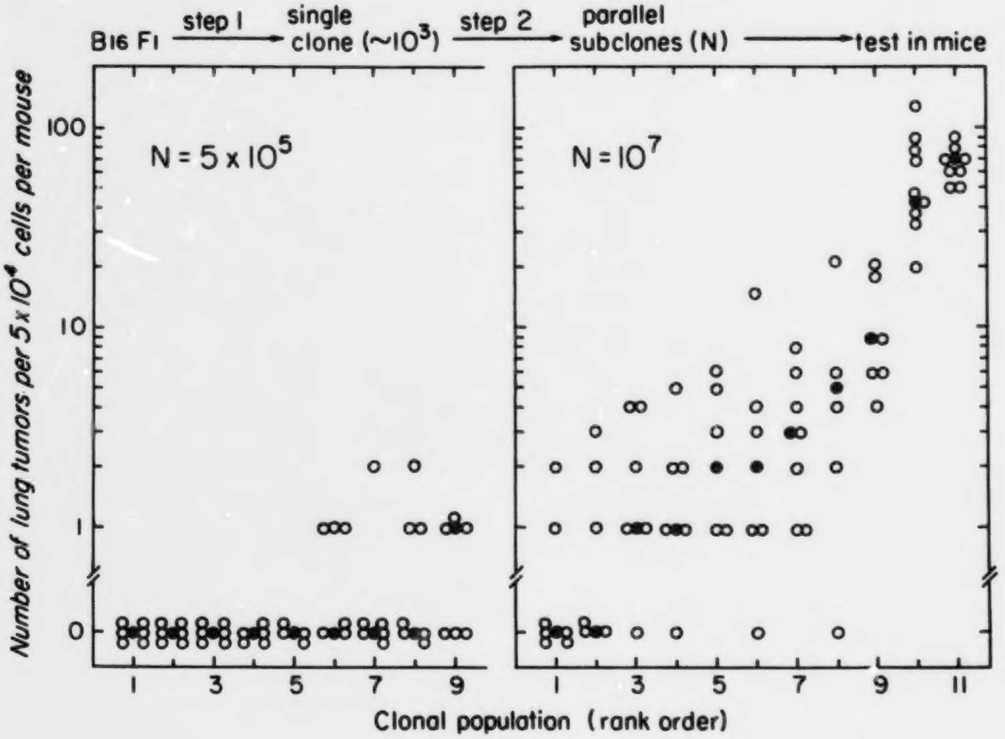

Figure 1. Variation in the number of lung metastases observed in mice injected with parallel subclones of B16F1 cells grown to different population sizes (N). A single B16F1 clone was grown to about 10^3 cells and was then further subcloned (step 2). Parallel subclones grown to population sizes of 5×10^5 cells or 10^7 cells were then tested in the experimental metastasis assay. Open circles show the number of lung tumors observed in individual mice when 5×10^4 cells per mouse were injected. Closed circles show the median mouse for each clone[1].

animal to animal differences appear to have only a minor effect on metastatic heterogeneity.

Treatment Of Metastasis

KHT Sarcoma cells injected intravenously form nodules almost exclusively in the lung. These nodules can be counted in treated and control animals to give good quantitation of the efficacy of a treatment. Alternatively, tumors growing intramuscularly seed lung metastases in a predictable manner so that the effects of treatment can be tested against spontaneously arising metastases. Recently we have been testing a bacterial product obtained from E.coli (a colicin or bacteriocin). This polypeptide has been found to be effective in killing KHT cells recently seeded into lungs by intravenous injection and to be active against spontaneously seeded metastases. Further studies are planned to establish its ability to kill larger metastatic deposits by treating mice at different times after tumor cell injection, and to determine its activity in combination with radiation and cytotoxic drugs against tumors growing intramuscularly.

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Radiation-Drug Combinations For The Treatment Of Solid Tumors

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The combination of partially effective treatment modalities in order to improve current cancer treatment regimes remains a major challenge to oncologists. We have been interested in developing a better understanding of the way drugs may be effectively used in combination with radiation for the treatment of solid tumors. We feel knowledge of the mechanism of action of drug-radiation combinations will allow a rational development of how they may be used. This work is dependent on discussions with a number of clinical colleagues in order to define problems and to determine the applicability of particular approaches.

■ The Study Of Agents With Selective Toxicity Towards Solid Tumors

As tumors grow they may outgrow their vascular blood supply and contain regions in which oxygen is at low levels. Cells in such regions are radiation resistant and represent a potential limiting population for the cure of solid tumors by ionizing radiation.

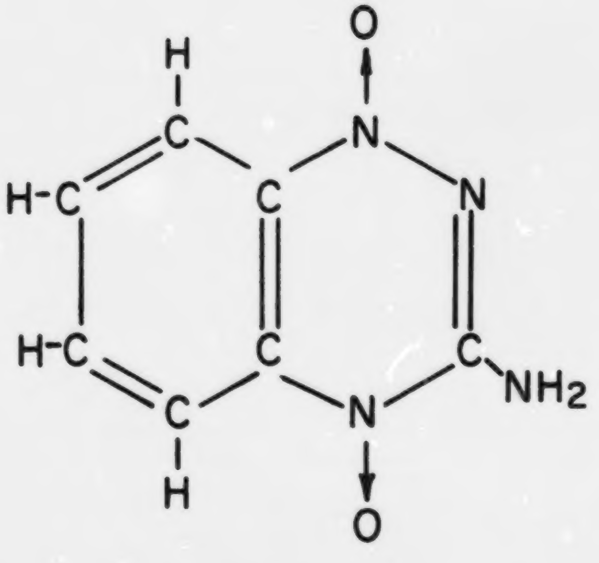

Figure 1. Structure of SR4233, a benzotriazene dioxide with selective toxicity towards hypoxic tumor cells.

Benzotriazene Dioxides (Laderoute, Lapointe, Rauth)

SR4233 (Figure 1) is a benzotriazene dioxide which has recently been shown by Brown and colleagues at Stanford University to be selectively toxic to cells at low levels of oxygen. This toxicity is caused by the increased metabolism of the drug to toxic intermediates in oxygen-deficient cells. We have been studying the mechanism of this process and the role of oxygen in preventing toxicity. Our evidence suggests a model in which the parent drug is reduced by the addition of an electron to form a radical anion. If even low levels of oxygen are present, it removes the electron thus restoring the molecule to its original form. In the absence of oxygen the radical anion chemically rearranges to form a new reactive radical form perhaps releasing a hydroxyl radical. This reactive radical form(s) can react with DNA causing breakage of the molecule. Analogues of benzotriazene molecules have been found which apparently form the initial radical but do not undergo the rearrangement to a toxic intermediate. Benzotriazene dioxides appear to be a novel class of hypoxic cell toxins with potential as chemotherapeutic agents and/or as markers for hypoxic cells in solid tumors.

Nitroimidazoles (Laderoute, Lapointe, Rauth)

Two-nitroimidazoles such as misonidazole and SR2508 have been and currently are under study as hypoxic cell-specific radiosensitizers and hypoxic cell toxins in clinical trials in radiotherapy[1]. We have been studying the mechanism by which they show selective toxicity towards hypoxic cells even in the absence of radiation. This work has been done in collaboration with Dr. R.A. McClelland of the Department of Chemistry at the University of Toronto. A number of metabolic intermediates of these compounds have been synthesized and tested for their toxicity towards cells. Recently the nitroso-intermediate has been synthesized and, though unstable under physiological conditions, has been shown to be strikingly toxic towards mammalian cells, suggesting that it may be the important intermediate in the activation of this class of drugs. The molecular nature of the damage caused by nitrosoimidazoles is currently under study.

Mitomycin C And Porfiromycin (Marshall, Rauth)

The cancer chemotherapeutic agent mitomycin C has been widely used for the treatment of a variety of solid tumors. It has been shown to have increased toxicity toward hypoxic compared to aerobic cells in tissue culture; this appears to be due to the enzymatic activation of these compounds to an intermediate chemical species whose ultimate fate is oxygen sensitive. We have developed methods which allow us to monitor the effect of oxygen on toxicity of mitomycin C using an extremely sensitive oxygen probe developed by Dr. C. Koch of the Cross Cancer Institute in Edmonton with whom we have collaborated in its evaluation. Using this probe we have demonstrated that possibly two mechanisms exist for activating mitomycin C, one of which is oxygen sensitive. The oxygen independent mechanism can be enhanced by the presence of vitamin C.[2] These studies suggest that oxygen and vitamin C may be important modifiers of drug toxicity clinically. Recently Dr. A. Sartorelli and colleagues at Yale University have shown that porfiromycin, an analogue of mitomycin C, has an even greater selective toxicity toward hypoxic cells than mitomycin C. Preliminary measurement of the oxygen concentration dependency of this toxicity have confirmed these results. A detailed comparison of mitomycin C and porfiromycin toxicity is being carried out to see if porfiromycin may be a superior analogue to mitomycin C for clinical testing. In collaboration with Dr. C. Erlichman we have developed a biological assay for active mitomycin C in patient plasma using a mutant of Chinese hamster ovary cells which is deficient in the repair of drug-induced crosslinking of DNA strands. The results of this assay indicate that the potentially active form of mitomycin C in patient plasma is the parent drug itself (Figure 2). No evidence for toxic metabolites was found. This assay may be useful for other chemotherapeutic agents especially those that cause DNA crosslinks[3].

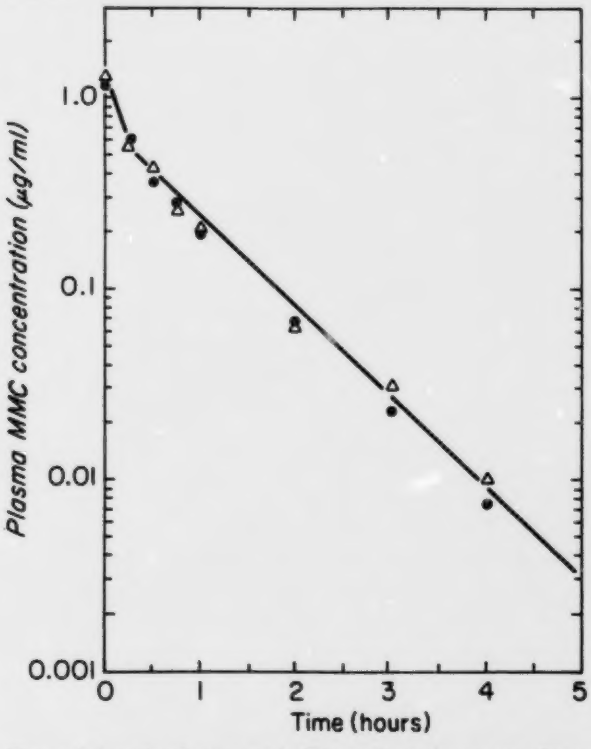

Figure 2. Levels of mitomycin C in patient plasma as a function of time after an intravenous injection of 15 mg/m². Closed circles: levels of mitomycin C measured by a high pressure liquid chromatography procedure. Open triangles: levels of mitomycin C measured by a newly developed bioassay.

■ Interaction Of 5-Fluorouracil (5FU) With Fractionated Radiation In The Treatment Of Squamous Cell Tumors (Weinberg, Lapointe, Rauth)

Clinical investigations are being carried out in our Institute by Drs. Cummings, Keane, Thomas and Dembo on four-day infusions of 5-fluorouracil, plus or minus mitomycin C, with standard fractionated radiation for the treatment of squamous cell tumors of the anus, head and neck, and cervix. In order to better understand the possible mode of interaction and optimal conditions for combining 5-fluorouracil and radiation, we have used a transplantable murine squamous cell tumor in mice. The drug alone is effective in causing tumor shrinkage. We have given the drug both as acute injections and as infusions over 3-14 days using mini-osmotic pumps. It appears infusion is the most effective way of giving the drug. Radiation alone, either as a single dose or fractionated, is effective in delaying tumor growth. When 5FU is given with fractionated radiation the tumor responds to both agents in an additive fashion, that is, the effect of 5FU in delaying tumor growth adds to the effect of the radiation. This model system appears to be a useful approach to better understanding the way 5-fluorouracil and radiation can be combined for more effective treatment of solid tumors.

■ Radioprotection Of Cells And Tissue (Davey, Rauth)

Tumors of the central nervous system, especially brain tumors, are particularly difficult to treat successfully with ionizing radiation. A limitation to potentially curative doses is damage done to surrounding normal tissue. Under the assumption that the limiting tumor cell population may be oxygen deficient (hypoxic) radioresistant cells, an alternative approach to sensitizing these cells to radiation is to protect the oxic cells while not altering the sensitivity of hypoxic cells so as to reduce the differential sensitivity between them. Initial experiments carried out *in vivo* in mice in Edinburgh indicated that 4-hydroxy sodium butyrate, a drug used clinically for treating head injuries, conferred some protection on cells in the sub-ependymal plate of the brain in rats exposed to ionizing radiation. Initial studies *in vitro* with established cell lines indicated that some protection from radiation damage of oxygenated hamster fibroblast cells occurred. Currently techniques are being established for the study of normal (glia) and malignant (astrocytoma) human brain cells in tissue culture to see if 4-hydroxy sodium butyrate is able to protect these cells under hypoxic or oxic conditions. The results of these studies should allow a better estimation of the potential usefulness of this drug in the radiotherapy of brain tumors.

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Molecular Mechanisms

The Cellular Phosphoprotein p53

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There is now good evidence that the cellular phosphoprotein p53 is involved in the transformation process. p53 protein is found in high levels in a wide variety of transformed cells. Overproduction of p53 protein in certain cells has been shown to confer an enhanced tumorigenic phenotype. Furthermore, expression of p53 together with activated c-Ha-*ras*-1 can transform rat embryo fibroblasts following DNA mediated gene transfer. Expression of p53 has also been shown to immortalize early passage cells in culture. Hence, p53 has oncogenic potential.

In addition to being associated with transformation and tumorigenicity, it has been suggested that p53 plays an important role in the cell cycle, particularly in the regulation of cell division.

The objectives of my research program are to define the role of p53 in neoplasia and to understand the mechanism(s) regulating p53 expression in normal and transformed cells. We have chosen three experimental systems in which to examine p53 expression: Friend virus-transformed erythroleukemic mouse cell lines, leukemic blast cells from patients with acute myeloblastic leukemia (AML), and cell lines derived from patients with lymphoma.

p53 In Friend Virus-Transformed Erythroleukemic Cell Lines

We have observed altered expression of the p53 gene in erythroleukemic cell lines, whereas in other cells, p53 protein cannot be detected. Southern blot hybridization analysis indicates that the p53 gene is rearranged and consequently inactivated in cell lines that do not synthesize p53[1]. In addition, we have determined that heterogeneity in p53 expression is associated with heterogeneity in tumorigenicity.

We are focussing our attention on two independent cell lines that do not synthesize p53 protein as a result of rearrangement in their p53 genes but do synthesize antigenically related proteins of 44,000 daltons (p44) and 46,000 (p46), respectively. p44 is synthesized as a result of a deletion in the p53 gene that removes N-terminal amino acid coding sequences. The truncated protein is unusually stable and accumulates to high levels intracellularly. Moreover, it appears to have undergone a change in conformation as revealed by epitope mapping studies. This study represents the first description of an altered p53 gene product arising by mutation during neoplastic progression and identifies a region in the p53 protein molecule that plays a role in determining p53 stability *in vivo*. Deletion of nucleotide sequences also appears responsible for synthesis of p46. Isolation and characterization of cDNA clones indicate that all of exon 7 and part of exon 8 is deleted. Intron 6 sequences immediately upstream of the deletion are retained in the p46 mRNA and code for six novel amino acids not present on p53.

p53 Expression In Leukemic Blast Cells From AML Patients[2]

To examine the involvement of p53 in human neoplasia, a study of p53 expression the leukemic blast cells of patients with acute myeloblastic leukemia (AML) was initiated. p53 protein was detected in the blast cells of 19 out of 34 patients but not in normal myelopoietic cells. We found a highly significant correlation between p53 protein synthesis in leukemic blast cells and the secondary plating efficiency of these cells. The latter provides an estimate for the self-renewal capacity of progenitor cells in the blast population. These data indicate that p53 may be involved in leukemic stem cell renewal. We propose to test this hypothesis directly. Retrovirus vectors will be used to introduce and express full length human p53 cDNA clones in blast cells. cDNA clones will be oriented in the vectors in both sense and anti-sense orientation in order to manipulate p53 expression positively and negatively. If the hypothesis is correct, expression of p53 in blast cells will increase their self-renewal capacity and inhibition of p53 expression will reduce their self-renewal capacity.

p53 will also be expressed in a number of other target cells. These cells will be examined for phenotypic changes including changes in growth properties, growth factor dependency and tumorigenic potential.

p53 Expression In Human Lymphoma Cell Lines

Ten out of eleven human lymphoma cell lines that we have examined express p53 protein. By quantitative radioimmunoassay, one of these cell lines has more p53 protein than SV40-transformed cells. In SV40-transformed cells, p53 forms a complex with the SV40 large T antigen. As a result, p53 protein is stabilized and its half life increases from 20 minutes in the unbound state to over 20 hours in the bound state. p53 protein is stable in the lymphoma cell line we have examined with a half life in excess of 10 hours. Hence, the increased stability of p53 protein appears responsible for the high steady state level of the protein. We wish to determine the mechanism leading to p53 protein stability and accumulation. Lymphoma cells provide a good experimental system inwhich to search for cellular proteins that may interact with and stabilize p53 during transformation. Alternatively, p53 protein may be qualitatively altered in these cells, possibly by mutation, resulting in increased stability. It is also possible that the intracellular environment of human lymphoma cells restricts the rapid turnover of p53.

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Studies On The Role Of Nuclear Factor I In DNA Metabolism

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Changes in the control of DNA replication and gene expression often accompany the transformation of cells to tumorigenicity. My research interests are in the control of DNA replication and the association between DNA replication and the expression of cellular genes. To gain insight into these processes, my laboratory is studying the site-specific DNA binding protein, nuclear factor I (NFI), which appears to be involved in both DNA replication and RNA transcription.

Nuclear factor I is a site-specific DNA binding protein that is required for the efficient replication of Adenovirus DNA *in vitro* and *in vivo*. NFI functions by binding to a specific site within the origin of Adenovirus DNA replication and stimulating the initiation of DNA synthesis. To determine the number of binding sites for NFI in human DNA, I developed a new technique, "protein-mediated selection", that permitted the isolation of fragments of human DNA that bind tightly to NFI[1]. This was the first demonstration that sites for a sequence-specific DNA binding protein could be isolated directly from unfractionated genomic DNA by their affinity for a protein. With this technique it was possible to demonstrate the existence of cellular NFI binding sites (FIB sites), to calculate the number of binding sites in the human genome (approx. 60,000), and to determine that both strong and weak binding sites are present in human DNA[1]. It was then possible to sequence three of the cloned binding sites and determine a consensus sequence, TGG$(N)_{6-7}$GCCAA, that is apparently necessary but not sufficient for the binding of NFI[2].

In my laboratory at The Ontario Cancer Institute, we are currently studying the sequence requirements for nuclear factor I binding to DNA. We have recently found that synthetic oligonucleotides can be used *in vitro* as binding sites for NFI[3] and have used this finding to determine some sequence and structural features important for the binding of the protein to DNA. We had previously shown that NFI binds to DNAs containing the consensus sequence TGG$(N)_{6-7}$GCCAA[2]. By making novel use of libraries of partially degenerate oligonucleotides, it was determined that NFI binds to 40-60 per cent of DNAs containing the sequence TGG$(N)_6$GCCAA but to only 4 per cent of the DNAs with the sequence TGG$(N)_7$GCCAA. Thus, the distance between the TGG and GCCAA motifs is crucial for the binding of NFI. Individual members of each of these libraries are now being studied to determine what DNA sequences or structures in addition to the TGG$(N)_{6-7}$GCCAA consensus sequence are needed for NFI binding to DNA.

Other studies in my laboratory include the reintroduction of cloned human FIB sites back into HeLa cells. We have generated long-term transfectants of HeLa cells using FIB sites cloned into the pSV2neo vector and are analysing these cell lines for the number of copies of the vector DNA. These studies should yield important information of the possible role of FIB sites in DNA replication and/or recombination. In addition, we are also restriction mapping and sequencing four newly cloned FIB sites isolated from the human genome. The information obtained should add to our knowledge of FIB site structure and distribution within the human genome.

We have also been investigating the possible role of FIB sites in the expression of cellular genes. We recently obtained the very exciting finding that the *in vitro* transcription of RNA from the adenovirus major late promoter is stimulated several fold by the presence of a cellular FIB site. The ability of a FIB site to stimulate transcription from a heterologous promoter in an *in vitro* system provides a functional assay for a binding site that does not require adenovirus-encoded proteins. This *in vitro* transcription system will be used to study the possible role of NFI and FIB sites in gene expression.

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Mechanisms Of Growth Factor-Regulated Gene Expression

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An understanding of uncontrolled proliferation of malignant cells in human cancers requires a detailed analysis of the regulation of expression of genes that control normal cell growth. The binding of growth factors to their specific cell surface receptors initiates a complex series of events that culminates in the proliferation of cells in culture. Treatment of the appropriate tissue culture cells with platelet-derived growth factor (PDGF) or epidermal growth factor (EGF) results in the rapid induction of expression of specific genes, including the cellular oncogenes, *c-myc* and *c-fos*, and the cytoskeletal β-actin gene. The induction of expression of these genes appears to be a primary consequence of the interaction of specific growth factors with their cognate cell surface receptors and is controlled, at least in part, at the level of transcription initiation. Since *c-myc*, *c-fos* and β-actin appear to play crucial roles in the control of cell growth, an understanding of the transcriptional regulation of these genes by growth factors would have broad biological implications.

We are investigating the molecular mechanisms involved in the induction of transcription of the *c-myc*, *c-fos* and β-actin genes in response to PDGF and HEGF. An *in vitro* approach, used previously to determine the DNA sequence and protein factor requirements for efficient transcription from the adenovirus-2 major late (Ad2ML) promoter, has been chosen to study the stimulation of specific gene transcription initiation by growth factors. Our objectives are to: (1) define the DNA sequences that are required for efficient and growth factor-inducible *in vitro* transcription of the *c-myc*, *c-fos* and β-actin promoters; and (2) identify and characterize the cellular components that are modulated by either PDGF or EGF treatment and are involved in the stimulation of *in vitro* transcription from the *c-myc*, *c-fos* or β-actin promoters. Recombinant DNA techniques have been used to introduce specific deletion and point mutations in the 5′ flanking sequences of the *c-myc*, *c-fos* and β-actin promoters; the effects of these mutations on transcription will be analyzed using reconstituted *in vitro* transcription systems prepared from serum-deprived and growth factor-treated cells. To ensure that the results obtained *in vitro* accurately reflect the *in vivo* situation, the transcription of the *c-myc*, *c-fos* and β-actin genes will be analyzed in serum-deprived and growth factor-treated cells in culture.

We have constructed and transcribed *in vitro* a series of wild-type and deletion mutant *c-myc*, *c-fos*, β-actin and Ad2ML promoter *in vitro* expression vectors. The RNA polymerase II-dependent RNA synthesized *in vitro* in extracts prepared from HeLa cells grown either in suspension or monolayer corresponded in size to RNA that initiated from the specific *in vivo* mRNA start sites for all the above promoters. Experiments are in progress to determine the culture conditions under which the transcription *in vitro* from the wild-type but not mutant *c-myc*, *c-fos* and β-actin promoters is increased in extracts prepared from growth factor-treated as compared to serum-deprived cells. We have also sequenced the 5′ flanking region of the β-actin promoter from -462 to -244; by DNA sequence comparison with the serum-responsive element of the *c-fos* promoter we have observed a short region of homology between the two promoters. To assess the potential role of these specific nucleotides in the growth factor-responsiveness of the *c-fos* and β-actin genes, we are generating libraries of substitution point mutations in the 5′ flanking region of the two promoters. These mutants will be analyzed for their ability to be efficiently transcribed in a growth factor-dependent fashion and to bind specific DNA binding proteins.

Results from this study will lead to a greater insight into the molecular events controlling the induction of specific gene transcription by growth factors, one of the steps involved in the pathway from the initial interaction of a growth factor with its receptor that ultimately results in cell division.

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Chemical Carcinogenesis

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The overall goal of this research program is to provide an experimental basis for understanding mechanisms underlying the biological response of an important class of chemical carcinogens, the nitrosamines. These are valuable compounds with which to study mechanisms of the chemical induction of cancer since they can induce tumors in many organs of numerous species. Additional interest derives from the occurrence of a number of nitrosamines in the environment, and their formation from precursors in the body. Nitrosamines, therefore, are prime suspects in the search for causes of human cancer.

Mechanism Of Tissue Specificity In Nitrosamine Carcinogenesis (Catz-Biro, Hirani-Hojatti, Milligan, Zucker)

A central problem in chemical carcinogenesis is that in addition to variations in strain and species response, the distribution of induced tumors amongst various tissues depends on the type of carcinogen used. The nitrosamines are an unusual class of carcinogen since they can produce tumors in a wide variety of organs. The tissue specificity, although affected somewhat by the dose of the nitrosamine, is not usually affected by the route of administration, and the susceptible tissue depends on the chemical structure of the nitrosamine. The mechanism for this organotropic effect is not understood. The goal of this research project is to investigate the mechanism by which nitrosomethylbenzylamine (NMBzA) specifically induces tumors of the esophagus in the rat, while the structurally related nitrosodimethylamine (NDMA) induces tumors of the liver. These nitrosamines do not concentrate preferentially in the target tissue. Our work has shown that the ability of the esophagus to activate NMBzA metabolically probably plays an important role in determining its carcinogenicity in that organ. In the liver, however, an organ in which NMBzA shows no toxic or carcinogenic effects, we also found extensive metabolic activation of this nitrosamine. Furthermore, NMBzA methylates hepatic DNA and forms the putative promutagenic O^6-methylguanine. Investigation of the potential genotoxic action of NMBzA in the liver, as well as the reasons for the differential cytotoxicity of this nitrosamine in the esophagus compared to the liver, forms the basis of our current research.

Induction Of Pancreatic Cancer By Nitrosamines (Boux, Giles, Zucker)

Carcinogenic nitrosamines normally undergo cytochrome P450-dependent α-hydroxylation as a first step in the reaction sequence leading to the production of an electrophilic alkylating agent which interacts with nucleophilic sites in DNA. A somewhat surprising feature of the biological reactivity of several simple nitrosodialkylamines such as nitrosodipropylamine (NDPA) is that in addition to direct transfer of an intact propyl group to DNA, the nitrosamine also acts as a methylating agent. We have found that important intermediates in this process are products of metabolic γ-oxidation on one side chain of the nitrosamine, and we have recently succeeded in elucidating the mechanism of the methylation reaction. Our research is now directed towards understanding the mechanism of action of derivatives of NDPA that are oxidized on the γ-carbon atoms of both propyl groups. These nitrosamines are unusual in that they induce tumors of the pancreatic ducts in the Syrian hamster. These tumors are particularly interesting because of their similarity to pancreatic cancer in man which is principally ductular in nature. As well as attempting to determine the mechanism of metabolic activation of these compounds and the mode of interaction of intermediates with DNA, we are using tissue culture techniques, isolated perfused organs, and intact animals to determine the mechanism of tumor initiation in the target cells of the hamster pancreas, and reasons why the rat pancreas is resistant to their carcinogenic action.

Activation Of Proto-Oncogenes By Chemical Carcinogens (Hirani-Hojatti, Gunhouse, Milligan)

Recent research has shown that certain genes which are present in our normal genetic make-up become altered in their structure or expression in cancer cells. Oncogenes of the ras gene family may be activated by single base pair substitutions of their non-transforming counterparts, the proto-oncogenes. Many carcinogens are potent mutagens and much evidence suggests that tumor initiation results from mutations arising from the binding of ultimate carcinogens to DNA. In another research program, we are investigating whether activated forms of nitrosamines can generate transforming oncogenes when they interact with proto-oncogenes, and whether different nitrosamines interact in a site-specific manner with these genes. Such reactions could be important in the initiation of carcinogenesis by nitrosamines and possibly in defining their species and organ specificities.

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Immunology

Development of Cytotoxic T Lymphocytes

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T cells seldom react with free antigen. Instead, they react almost exclusively with antigen presented on the surface of another cell. They then recognize not only the antigen (foreign) but part of the cell presenting it (self). The self components recognized are coded for within the MHC (major histocompatibility complex). This dual specificity for foreign and self is the phenomenon of MHC-restriction. It is difficult to see how a specificity repertoire with this property could develop through an essentially random process as seems to be the case for B cells.

Cells committed to the T lineage develop from stem cells in the bone marrow. These then normally migrate to the thymus for further development and it is here that almost all efforts of others is currently focussed. We, however, believe that, at least for cells reactive against or restricted by class I MHC products, the most essential steps in shaping the specificity repertoire develop from precursors which are initially reactive against self-MHC. Two testable predictions follow from this hypothesis: first, it should be possible to find large numbers of immature T cells capable of recognizing self-MHC and, secondly, there must be a mechanism for preventing such cells from becoming cytotoxic effector cells. We have evidence supporting both predictions.

We have developed a limiting dilution microculture system in which stem cells in bone marrow give rise to autoreactive cytotoxic effector cells carrying T cell markers and specific for class I MHC markers. Current and future work on these cultures have two objectives: (1) manipulate the environment of the culture to see if reactivities other than anti-self can be developed and to test directly whether they develop from an initially self-reactive state; and (2) develop the technology to look for gene expression at the mRNA level in the rather small number ($\approx 10^3$) of cells available. The hypothesis that T γ genes are involved in self-reactivity is particularly intriguing and we currently find that colonies containing autoreactive cells also contain cells expressing γ mRNA. In related studies, we have shown that the T cell specificity repertoire appears to continue to develop and diversify under the control of the environment during an ongoing immune response. We would like to analyze these rapidly diversifying cultures for changes in gene expression. This requires that we obtain fairly large numbers of cells of a single intermediate specificity for analysis with the molecular technology mentioned above. We are presently investigating whether T cell hybridomas will satisfy this requirement.

Some years ago we discovered that some cells have the physiological property that when they are recognized by activated precursors of T effector cells, the T cell becomes inactivated, a phenomenon we have called the veto phenomenon. This mechanism could prevent the activation of T cells reactive against self-membrane compounds (including self-MHC and foreign antigen in association with self-MHC). A major advance in our understanding of the veto phenomenon was the discovery that cloned CTL lines invariably have veto activity i.e. they can delete CTL precursors capable of recognizing the MHC antigens carried by the CTL line without regard for the recognition capabilities of the line. The *in vitro* maintenance of CTL lines requires that they be cultured continuously with both the appropriate stimulator and IL-2; omission of either usually leads to rapid death of the line. We have discovered that some CTL lines, when cultured without appropriate stimulator, become autoreactive with specificity for self-MHC while simultaneously losing veto activity. Consequences of this observation are still being explored. We have previously shown that veto activity maps to self-MHC and have now completed very extensive studies showing that veto activity maps to self-class I MHC and showing explicitly that self-class II MHC is not involved. Studies showing that veto cells suppress only activated, and not resting CTL precursors (a prediction of our model) have been completed.

Somehow, the environment can affect T cell specificity in a very rapid way. One possibility is that cell surface sugars, lectins, and glycosyltransferase enzymes play a role. We continue to accumulate evidence supporting the concepts that (i) some aspect of T cell recognition has lectin-like properties and (ii) that the pattern of cell surface glycopeptide extracts from three MHC-different (H-2^{d}, H-2^{k}, H-2^{b}) murine tumor cell lines can inhibit allorecognition by CTL in an MHC-specific manner and that inhibition of N-linked glycosylation (with tunicamycin) reduces the ability of a target cell to be recognized. As a further direct confirmation of these ideas, we have shown that a glycopeptide extract prepared from L cells (H-2^{k}) transfected with a K^{b} class I gene can inhibit CTL recognition of K^{b}-expressing target cells. Current work is concentrating on developing a very rapid, quantitative, cytotoxicity assay to enable one to characterize the inhibitory components in a glycopeptide preparation, and an investigation of the effects on T cell recognition of other glycosylation inhibitors (deoxynijiromycin, swainsonine).

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T Cell Antigen Receptor

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T lymphocytes are selected in the thymus before maturing into distinct subclasses of functional T cells. Presumably, the selection process is based primarily on the specificities of the surface T cell antigen receptors. Regulation of expression of these T cell antigen receptor genes and the manner by which they are selected or "educated" are, therefore, two of the key questions in modern immunology. In this proposal, we have described several projects aimed at answering these questions. Studies involving transgenic mice carrying T cell antigen receptors with specific reactivities to either self MHC genes or antigen-specific MHC-restricted reactivities will be performed. The selection by the thymus of cells carrying these receptors will be analyzed and monitored. In addition, experiments are also designed in an attempt to answer questions pertaining to the factors involved in the regulation of expression of the T cell γ chain genes and at elucidating their possible functions.

Haemopoiesis

The Blast Cells Of Acute Myeloblastic Leukemia: A Laboratory-Clinical Study

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Abnormal hemopoietic clones in patients with Acute Myeloblastic Leukemia (AML) contain characteristic populations, morphologically identified as blast cells. These may be considered as abnormal lineages, derived originally from hemopoietic stem cells or their earliest descendants, and maintained independently by progenitors with stem cell properties. The research goal is to examine this blast lineage both because of its intrinsic importance in AML and as a model for human cancer generally.

Regulatory mechanisms affecting the growth of leukemic cells are attractive targets for new treatments. The blast cells of Acute Myeloblastic Leukemia (AML) are useful tools for exploring this approach. These malignant cells may be considered as a lineage; a minority are stem cells capable of both self-renewal and determination followed by terminal divisions ending in proliferatively-inert cells retaining blast morphology. Two cell culture methods are available for the study of blasts. The first is a clonogenic assay. Blast stem cells form colonies in methylcellulose provided growth factor(s) present in media conditioned by the bladder carcinoma cell line HTB9 (HTB9-CM), are included in the cultures. Most of the cells in colonies are terminal blasts, incapable of division. A minority (<1) can be replated successfully. Thus the clonogenic assay shows primarily post-deterministic events in blast differentiation. Blast progenitors will also grow in suspension, provided the cell density is high and HTB9-CM are present. In these cultures blast progenitors increase in number, reflecting their self-renewal capacity. The requirement for high cell density can be met by preparations of blast cell membranes. Evidence is also available that specific genes may be involved in the self-renewal process. Thus, three forms of growth regulation, similar to those encoded by proto-oncogenes, can be shown to be operative in AML blast cell cultures.

Recently progress has been made in the following specific projects:

A Clinical Trial Of High-dose Ara-C

A clinical trial has been completed of high-dose ara-C for both remission induction and maintenance. The trial was closed after the accrual of 43 patients. We were able to collect biological data on all but two. Briefly, the treatment protocol consisted of ara-C at a high dose ($3G/M^2$) twice daily for 6 days for induction and the same drug at conventional doses ($100mgm/M^2$) for maintenance. The schedule was adopted because it had been proven safe as second line treatment and because the culture studies indicated that ara-C might have inhibit self-renewal divisions more efficiently than terminal divisions. The trial was designed to seek answers to certain questions: will self-renewal remain as an important attribute contributing to outcome when a single drug is used, one that may affect the renewal process? Will in culture measurements of ara-C sensitivity prove predictive for response when only that single drug was used? Would resistance to ara-C emerge when the same drug was used for both remission-induction and maintenance? The analysis showed that the response rate was 67% compared with 50% in the previous trial of a treatment protocol consisting of doxorubicin, ara-C and 6-thioguanine in combination. The number of complete remissions was increased (p=.01). However, survival was not prolonged significantly. These data showed that a single drug produced results that were not worse than those achieved with multi-drug regimens. No laboratory evidence was obtained for the emergence of drug resistant populations. The association of PE2 with successful remission induction was strengthened, compared to the previous trial; however, PE2 was not a significant contributor to the duration of survival. These data are consistent with the hypothesis that remissions were obtained with high-dose ara-C in patients that would have failed previous multi-drug regimens, but that these remissions were short-lived.

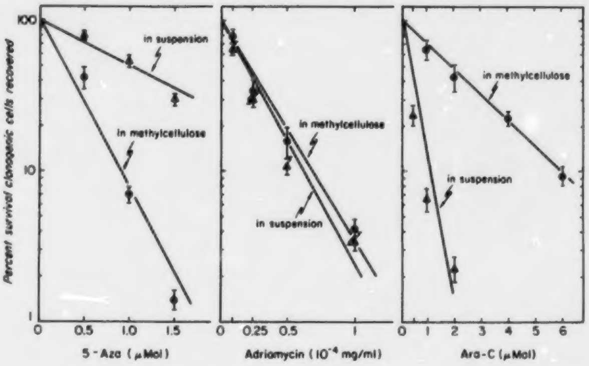

Figure 1. Survival curves for cells exposed to 5-aza (left panel), adriamycin (middle panel) or ara-C (right panel) either in suspension or in methylcellulose. In the former instance, the drug was included in the cultures used for colony-formation. In the latter instance, the drug was present during 7 days of suspension culture; the cells were then washed and tested for colony-formation in methylcellulose. The number of clonogenic cells per culture was calculated from the number of nucleated cells recovered from the 7 day cultures and the plating efficiency.

A Proposed Method of Selecting Anti-leukemic Drugs

As indicated above, we consider that ara-C may be useful in the treatment of AML because it has some specificity for mechanisms needed for blast cell renewal. We have noted also that the suspension culture assay for AML blasts reflects self-renewal more accurately than the clonogenic assay. Accordingly we tested the sensitivity of blast cells to ara-C using both the suspension and clonogenic assays. We observed that the cells appeared more sensitive to the drug in suspension than in methylcellulose, a finding consistent with the hypothesis that ara-C inhibits self-renewal selectively. The concept was tested by repeating the survival curves using the drug 5-azacytidine. This agent was chosen because, using the clonogenic assay, it appears to favor self-renewal; hence its action is opposite to that of ara-C. The comparison of survival curves for blasts treated with 5-azacytidine in suspension or using the clonogenic assay showed that, in contrast with the similar comparison for ara-C, the blasts less sensitive in suspension than when colony-formation in methylcellulose was the endpoint. A third drug, adriamycin was also tested, since this agent does not effect self-renewal as measured using the clonogenic assay. For adriamycin identical survival curves were obtained in suspension and using the clonogenic assay. Thus, a comparison of the sensitivities of drugs in suspension and in the clonogenic assay discloses three classes of response. First, very similar survival curves may be obtained under both conditions. Second, the cells may be more sensitive in suspension than in the clonogenic assay. Third, the reverse may be found, with colony-formation more sensitive than growth in suspension. These three classes of survival curves are illustrated in the Figure (Figure 1), were the same cells that were tested at the same time for each of the three drugs, either in suspension or using the clonogenic assay. We suggest that drugs of the second class, those that may have some specificity for self-renewal, may, like ara-C, be useful in the treatment of Acute Myeloblastic Leukemia.

Molecular Evidence for Linear Infidelity

We have used non-immunological methods to detect, within leukemic clones, expression of differentiation program components usually associated with more than one lineage (lineage infidelity). We examined the DNA from 24 AML patients using Southern blots following digestion with a variety of restriction endonucleases. Evidence of incomplete clonal T cell gene rearrangement was found in three instances, and in one, similar changes were found in immunoglobulin genes. These results show that our findings of doubly-marked blasts using immunological reagents should not be dismissed as artifacts of the method. It remains possible, however, that the apparently abnormal phenotypes may be found in very rare, predeterministic normal cells.

Growth Factors for Blast Stem Cells

In our studies of the effects of hemopoietic growth factors on AML blasts, we were fortunate in obtaining the collaboration of Dr. Steven Clark and Dr. Gordon Wong of the Genetics Institute (GI) in Boston. They had libraries available and transfection systems, using monkey COS cells as recipients. Screening of transfectant supernatants identified several with activity on blast progenitors. However, all of these were shown to contain GM-CSF. We proceeded to use this information for preliminary assessments of the effects of recombinant GM-CSF on blast cells, using both growth assays and the generation of adherent cells. GM-CSF was active by all three criteria; however, even with a limited number of examples, variation in dose response curves was found. Usually GM-CSF was less effective in promoting colony-formation than HTB9-CM, but equally active in both the suspension culture assay and in the production of adherent cells. We concluded that GM-CSF is an active growth factor for blast stem cells, but that full expression of their potential requires at least one additional factor. Wong and Clark of GI made recombinant G-CSF available; we found striking syngergism when GM-CSF and G-CSF were tested in combination for their capacity to promote growth of blast cells in methylcellulose or in suspension. It remains to be seen whether the full activity found in HTB9-CM can be explained by these two factors or, alternatively, if additional stimulators are active on blast cells.

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Clonogenic Progenitor Cells In Human Malignant Non-Hodgkin's Lymphoma

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Bone marrow transplantation has developed into a treatment modality with curative potential for patients with hemopoietic malignancies and other bone marrow deficiency disorders. Failure of the procedure may be related to three problem categories: infections, graft-versus-host disease and recurrence of the underlying malignancy. We have focused our interest to study mechanisms involved in the cellular reconstitution of transplanted bone marrow, and mechanisms involved in the control of malignant cell populations as studied on the model of clonogenic lymphoma cells.

The reestablishment of hemopoiesis after bone marrow transplantation appears to be a multi-factorial process involving donor and host parameters. Our studies have shown that the total number of nucleated cells in the bone marrow transplant inoculum influence survival while the number of clonogenic precursors have no effect. This observation raised the question whether or not currently available clonogenic assays are able to detect cell populations that are responsible for sustained bone marrow reconstitution, or whether auxiliary cell populations in the graft are mandatory for the appropriate function of clonogenic precursors. A search will continue using newer cell separation techniques and recombinant growth factors to identify earlier precursors and to monitor and modulate the engraftment process.

Besides the donor related parameters, we observed that the frequency of megakaryocyte colony forming cells (CFU-M in host) before initiation of ablative regimens predict the time of engraftment. While it is not likely that the cell population reflects the behaviour of primitive hemopoietic stem cells, it may measure host conditions that permit the growth of CFU-M *in vivo* before and after transplantation. This view is supported by the observation that growth factors in the plasma of bone marrow transplant recipients contain growth factors that correlate with time to engraftment. Studies will continue to determine the cellular source of these molecules and identify whether they are of donor or host origin. In addition, attempts will be made to characterize the activities and compare them to recombinant growth factors. These studies will lead to a more detailed understanding of the engraftment process and will determine whether or not either the host or the bone marrow transplantation inoculum could be manipulated to further improve the engraftment process.

The problem of disease recurrence after allogenic bone marrow transplantation is related to the inability of ablating tumor promoting malignant cell populations. In addition, it may also demonstrate the inability of reestablished bone marrow to control minimal residual disease. In order to address these questions, we have developed a model system in malignant lymphoma. Culture conditions are available that promote growth of clonogenic lymphoma cells in some patients with intermediate and high grade malignant lymphoma. The resulting colonies can be routinely recloned and established as EBV-negative cell lines with stable B-cell phenotype. The cell lines show the same immunoglobulin gene rearrangement pattern as that observed in the primary lymphoma sample. In addition, a significant clinical correlation was observed between culture data and clinical outcome. Patients that formed lymphoma colonies survived for a significantly shorter period of time than patients who did not give rise to colonies. These observations validate the use of the established cell lines as a model for human lymphoma to study mechanisms that control the proliferation of lymphoma cells and to develop criteria that may help to select patients for early bone marrow transplantation as well as improve the transplant procedure. For this purpose, clonogenic lymphoma cells and their growth promoting signals will be characterized by different methods.

Effects of Exogenous Oncogenes on Murine Hemopoietic Precursor Cells

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Our research is focussed on the mechanisms which control the growth, self-renewal and differentiation of the precursor cells which originate blood cell production in the mouse model.

Little is known of the extracellular factors required by primitive hemopoietic precursors for growth and self-renewal. IL-3 is sufficient for growth and differentiation of some pluripotential precursors in culture. However, we have found that more primitive cells having extended self-renewal potential require other factors in addition to IL-3 for their survival and growth, and that the additional factors can be found in medium conditioned by plastic-adherent cells from bone marrow. Cloned and immortalized adherent marrow cell lines have now been derived which secrete the essential factors. Characterization and identification of the factors, and assessment of the relationship between the responding cells and the primitive stem cells responsible for long-term maintenance of hemopoiesis *in vivo*, are currently in progress.

Intracellular mechanisms governing self-renewal and differentiation of primitive hemopoietic precursors have been difficult to study because of the scarcity of the early cells. However, exciting new opportunities for their study are now offered by advances in virology and recombinant gene technology. Cloned oncogenes influencing differentiation and self-renewal in other systems are available for examination of their effects in hemopoietic cells. Retroviral expression vectors provide a means of transducing these genes with high efficiency even into precursors that are rare. Temperature-sensitive oncogene mutants and inducible promoters offer the possibility of turning the expression of transduced genes on and off at will. Experiments are now underway using oncogenes to probe and manipulate the key functions of early cells, with a view in the shorter term to determining their effects in stem cells, and in the longer term to developing new tools for the direct molecular analysis of hemopoietic stem cell function.

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Health Status Indices and Biostatistics

The Logistic and Log Linear Models In Biomedical Applications

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The application of statistical techniques to medical and biological data is often quite challenging. Small samples, missing data, complex relationships between outcome and predictors, and nontrivial measurement error in the explanatory variables are not uncommon in this field. Although there is a wide assortment of techniques for dealing with these problems when the data is amenable to classical (normal) linear models, this is not the case when the response is binary.

Logical linear models play an important role in the statistical analysis of clinical research data. In laboratory research as well, it is best dealt with by applying logistic or log linear models. This research program aims to address issues of relevance to the application of logistic and log linear models in the content of clinical and laboratory research. We are currently developing simple methods for identifying the nature of the relationships between response and predictors. Also, we are examining the properties of general procedures for establishing the impact of measurement error of predictors in inference. The third component of this program refers to planning experiments, with particular emphasis on assays that are carried routinely, and for which previous experience is available.

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Research In Biostatistical Methodology

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Research activities are being conducted in two general areas: methodology for the statistical analysis of medical data; and medical decision-making.

Group Sequential Testing (Tsiatis, Rosner, Tritchler)

Group sequential tests for the analysis of survival data allow early termination of a study if large treatment differences occur. They thus preserve scientific rigor while allowing the explicit recognition of ethical considerations. In a recent paper[1], the distributional properties were derived for a group sequential test for treatment effect in the presence of other covariates in a randomized clinical trial. Investigation of the operating characteristics of these tests indicated that adjusting for significant covariates results in virtually no loss of power.

The Three-Decision Problem in Medical Decision-Making (Emerson, Tritchler)

A methodological paper describing some implications of decision theory for medical research is in press[2]. It asserts that medical researchers face decisions that require choice from among two or more alternatives, but traditional hypothesis tests offer an incomplete solution to the problem. A two-sided hypothesis test can only indicate whether two treatment effects are equal or unequal, whereas the decision to be made must specify which treatment, if any, is superior. We suggest that the problem is best posed as a three-decision problem in a decision-theoretic formulation. The decision-theoretic approach may be used to interpret and clarify current practice and the pragmatic and explanatory views of medical decision-making.

A Belief Function Approach to Paired Comparisons (Tritchler, Lockwood)

The task of ranking several objects with respect to some measure such as preference often occurs in medical decision-making. The task is difficult to do directly for more than a few objects, so the method of paired comparisons is often employed to determine a ranking. This method decomposes the task so that only two objects are considered at a time, and the judge simply chooses the "best" of each pair. The decomposition of the task not only simplifies the comparisons to be made, but also adds a new dimension to the data: the judge may contradict himself by intransitive patterns of choice. That is, he may prefer a_1 to a_2, a_2 to a_3, but a_3 to a_1. Thus measures of circularity have been developed to assess the performance of the judge.

It is usually the case that some choices are more difficult than others, and it is appealing to try to use information about the difficulty of the various choices. One possible approach is to elicit an intensity of preference. However, such information is very difficult to elicit, and may be inappropriate; the judge may be indecisive about a choice not because of a small perceived intensity, but because he realizes his comprehension or evidence is incomplete.

A similar approach is to obtain, for each comparison, a subjective probability distribution over the two possible preferences. However, this will not be a natural quantity to construct, and in many applications belief functions are more natural for describing the uncertainty about the comparisons. We are applying concepts from the theory of belief functions to the analysis of paired comparison experiments. The procedures obtained address similar issues as standard techniques, while offering a different perspective and new generalizations.

The theory of belief functions is a mathematical theory for the numerical assessment of uncertainty. The elements of the theory were set forth by Dempster in the late 1960's. Shafer further developed the theory and presented it as a general theory of evidence. The theory encompasses a rigorous formalism along with a set of concepts to assess uncertainty with incomplete evidence.

We apply the theory by considering each comparison to reflect an independent piece of evidence about the rankings. The object of the analysis is to construct a measure of the judges belief in sets of rankings of the objects. Dempster's rule of combination which is fundamental to the theory, is used to combine the information from the separate comparisons. We find that the belief function analysis allows an even finer decomposition of evidence than provided by the decomposition into pairs. The application of Dempster's rule also supplies a measure of circularity analogous to existing measures.

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Research On Quality of Life

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There are two main aspects of research on the quality of life. The first is concerned with ways to describe the quality of life. The second is concerned with ways such information may be used in decision making. In our recent work, the second aspect has been receiving increasing attention. Both aspects often have, as an underlying theme, the development of ways to help patients to participate in decisions about their own health.

It is well known that the way people react to decisions involving trade-offs, such as trade-offs between the quality and quantity of life, depends very strongly on the way information about the trade-offs is presented. For example, people have been asked to choose between two hypothetical treatments that differ in the extent to which a better expected duration of survival is exchanged for a poorer expected quality of life. Their preferences have been found to be dependant on whether the information about expected quality of survival is expressed in terms of mortality rates, or in terms of survival rates, even though these are simply two different ways of presenting exactly the same information. We have recently studied this "framing effect", and have obtained evidence that, when people are provided with mortality rates, and no information about survival rates, they may tend to take a pessimistic view about duration of survival, and assign a greater importance to quality of life.

Trade-offs between quality and quantity of life, like many uses of information about quality of life, involve conflicting values. Where values are in conflict, ethical problems arise. One example of a situation where values are in conflict is the randomized clinical trial; patients are asked to let chance, rather than their own preferences, determine which treatment will be chosen. The ethical implications of this situation have received a good deal of discussion, but little use has been made of quantitative empirical approaches. We have carried out a study to examine reasons why patients are or are not offered entry into clinical trials, and to compare, using quantitative methods, the perspectives of oncologists, nurses and family physicians. For oncologists, the main issue was quality of the scientific design of the trial. In contrast, nurses and family physicians gave relatively more weight to possible detrimental effects on the doctor-patient relationship. We concluded from this study that ethical issues, such as those that arise in clinical trials, or those that may arise when information about quality of life is used in decision making, can usefully be approached using empirical methods. We have also pointed out the need for the use of quantitative approaches to preference assessment to examine health-related decisions involving ethical dilemmas.

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Applications of Decision Theories in Oncology

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There is widespread interest in developing ways to encourage increased participation by patients in medical decision making. There are a number of recent and current research efforts at the OCI/PMH designed to address this interest.

Our current work involves: a) determining the relationship between cancer patients' preferences for information, their decision-making style, their perception of the cost/benefit tradeoffs associated with particular treatment protocols, and their willingness to participate in controlled clinical trials incorporating those protocols; and b) assessing the effectiveness of using aids adapted from the decision sciences to promote information comprehension and retention when seeking informed consent from cancer patients to either enter or refuse entry into a controlled clinical trial.

Our work for the future involves: a) determining the extent to which cancer patients' reports of the relative desirability of their current health state is a function of their evaluations of the health state they expected to experience and their comparisons with other health individuals; and b) testing the assumption that reports of the desirability of various health states are stable — an assumption that is fundamental to the valid use of these judgments in formal prescriptive decision analysis.

The rationale for these proposed studies rests upon the unanticipated results obtained in a recent OCI/PMH study of the relationship between patients' actual health status and health values. The results indicated that, across the entire study group, there was no direct overall relationship between general health status and health values. However, health status and health values differed according to membership in different sub-groups in the sample. One interpretation of the results described above is that the sub-groups, when providing health status and value self-reports, may use quite different frames of reference when responding to the same measurement tools at one point in time, and furthermore, that the frame of reference itself shifts across time.

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Influence Of The Mind On Cancer

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There is considerable, converging evidence, from three quite separate areas of research, for an impact of psychological events on the development and progression of cancer; (1) animal experiments, showing that stress may promote cancer growth and that mental expectations affect immune responses; (2) a large, although somewhat contradictory literature correlating personality in humans with cancer acquisition; (3) a number of clinical trials, mostly uncontrolled, claiming prolongation of life as a result of various psychotherapies.

Our research aim is to test the ability of group cognitive behavioral therapy to (a) improve mood (relieve anxiety and depression), and (b) prolong life in cancer patients. The therapy consists of training in relaxation, positive mental imagery, and cognitive restructuring including goal setting. The first aim has been accomplished: patients show a clinically and statistically significant improvement in mood (relief of anxiety and depression) as a result of attendance at the basic 7-session course. In a randomised control design this improvement was consistently better than that produced by a control (discussion only) intervention, although the statistical significance of the difference was marginal. Future work in this area will involve determining what psychological factors predict benefit from the behavioral therapy. To test hypothesis (b), that this kind of adjunctive therapy may prolong life, we will first conduct a case-control study, comparing outcome in patients participating in the group program with that of matched non-participants.

In parallel with the more practical group work, an attempt is being made to develop a simple theoretical scheme which will rationalize the effects of psychological, social and spiritual/existential levels of stimuli in health and disease. Interaction between levels of an individual may be most helpfully viewed in terms of information transfer, rather than as specific mechanisms. The central idea is that adequate information "flow" between levels, e.g. between the various levels of the body and conscious and unconscious mind, and between mind and social levels, is essential for maintenance of health. The mode of therapy that we are testing may be conceptualized as an attempt to promote optimal information flow or "connectedness" between the many organizational levels of the person.

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Imaging Research

X-Ray Imaging Research Program

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In the last decade we have witnessed an unprecedented growth in the development of new imaging systems in diagnostic radiology, e.g. CT, ultrasound, digital radiography, and magnetic resonance imaging. These techniques are revolutionizing diagnostic radiology as they provide information never before available. The development of new techniques as well as the improvement of existing techniques appears likely to continue. In all of this work the quest is to optimize the information content in the images or to present to the radiologist new information not available by other techniques. This must be done with minimal risk to the patient, whether from x-radiation or other agents.

The main focus of our work is in developing improved methods of diagnostic imaging for the early detection of cancer. Our research is organized into the following projects:

a) Research and development of scanned projection digital radiographic imaging systems;
b) Application of dual energy techniques in order to obtain more quantitative information;
c) Collaborative projects with other groups in the Physics Division; and,
d) Development of devices for quality assurance in diagnostic imaging.

■ Scanned Projection Radiography (SPR)

Mammographic Imaging System (Yaffe, Fenster, Nishikawa)

In previous work [1,2] we have documented the limitations of conventional film imaging for detection of breast cancer. These limitations are related to the limited dynamic range of film, the inflexibility of the display contrast scale, the reduction of signal-to-noise ratio due to structural granularity in the film and the dose efficiency of conventional mammographic film systems. We are developing a digital imaging system (Figure 1) which promises to overcome these limitations.

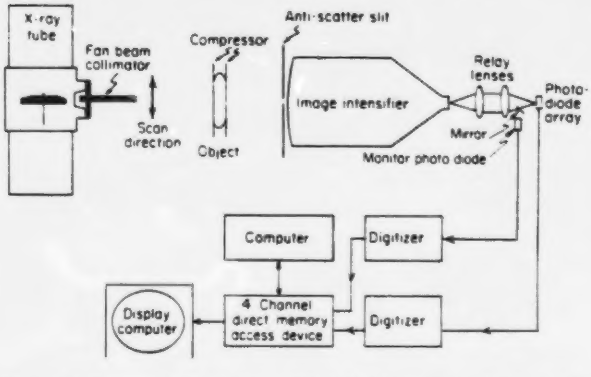

Figure 1. Scanned-Projection Digital Mammography System

A detailed evaluation of the signal-to-noise properties of the system has indicated that such a system should provide images with comparable or better signal-to-noise ratio than conventional film-screen systems and with significantly improved contrast. We have verified these predictions qualitatively by imaging contrast-detail detectibility phantoms and mastectomy specimens and compared the results with film images. Work to further optimize the digital system is currently underway.

Xenon-Detector for Chest Radiography (Fenster, Cardinal)

We are developing [3,4,5] a new multi-element ionization detector for SPR chest imaging. This detector array has high spatial resolution, is dose efficient and is easy to construct (Figure 2). It consists of two plates separated by a 2 mm gap filled with xenon at 30 atm. One plate is the high voltage electrode and the other is etched to form an array of conductive strips (0.5 mm centre-to-centre) focussed on the x-ray source. Present work is aimed at increasing the resolution by about a factor of two. The detector with these modifications will be evaluated for chest radiography by imaging chest, contrast-detail and dual energy phantoms.

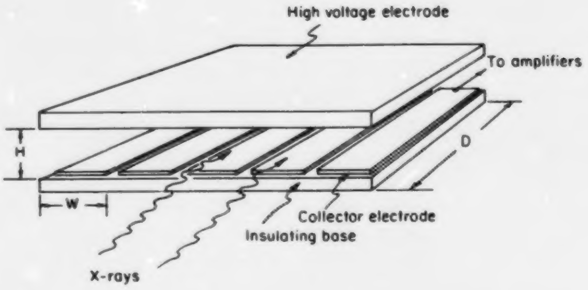

Figure 2. Schematic diagram of the xenon detector designed for scanned projection digital imaging.

■ Dual Energy Imaging

Chest Radiography (Fenster, Cardinal)

Detection of low contrast lesions using conventional radiographic systems suffers from high contrast obscuring shadows. These shadows are primarily caused by air/soft tissue or bone/soft tissue interfaces overlying the region of interest. Dual energy imaging allows the cancellation of a single material (such as bone) from the clinical image, and thus removes its obscuring shadow. The application of dual energy imaging is particularly promising in chest radiography as it is possible to eliminate superimposed bone shadows.

Bone cancellation in chest radiography has been demonstrated by others using a dual-kVp technique in an SPR system. These systems scan the patient twice at different kVp's and obtain two images. Since SPR systems require a few seconds to produce a single image, the collection of two images would result in serious misregistration of the two images due to patient motion. A better method would make use of an energy-sensitive detector. Techniques for dual energy imaging in CT using an energy-sensitive xenon ionization detector were investigated in this laboratory a number of years ago. We are using the dual-energy techniques already developed in our laboratory for CT[6,7] and our more recent developments in the design and construction of xenon detectors [3,4,5] for SPR imaging to develop an energy sensitive detector (split detector) for SPR digital imaging.

Mammography (Yaffe, Johns)

It is possible that more information about the status of breast tissue can be revealed *in vivo* by performing energy-selective imaging of the breast. Different types of tissue have not only different x-ray attenuation at one energy but also different energy dependence of attenuation. This information can be exploited [8,9] to characterize tissues and produce hybrid images which may aid in diagnosis of disease. One example is an image in which the detection of microcalcifications (generally considered as a premalignant lesion) can be enhanced by appropriate manipulation of the dual-energy images.

■ Collaborative Projects

Physical Characterization of Breast Tissues (Yaffe, Johns)

Specimens of breast tissue obtained from surgery and autopsy have been characterized in terms of x-ray attenuation, for the range of energies used in diagnostic imaging[10]. At all energies, infiltrating-duct carcinomas and fat are well distinguished by x-ray attenuation. For photon energies used in conventional mammography, tumors are more attenuating than normal fibrous tissue, while at higher energies, the ranges of attenuation overlap. The difference in attenuation between tumors and normal fibrous tissue may only be detectable using a digital-imaging system, since the contrast may be too low to be readily perceivable on a conventional film. Our results suggest that dual-energy imaging, in which two images of the patient are obtained at different x-ray energies and then subtracted, may be able to improve the detectibility of tumors, by allowing them to be isolated from the background structure of the image (Figure 3).

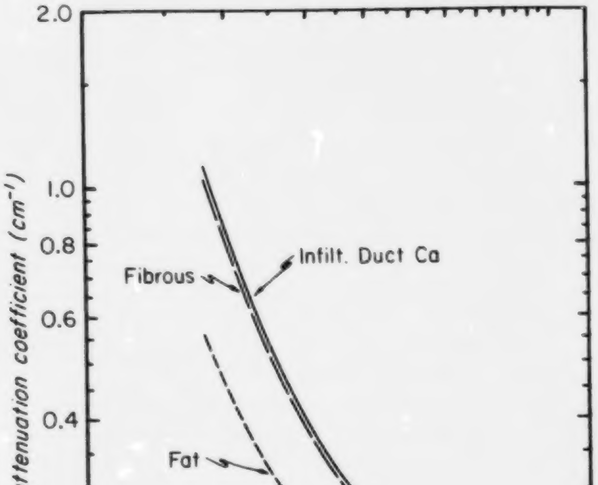

Figure 3. Average values of the linear attenuation coefficients for fat and normal fibrous breast tissue, and for infiltrating duct carcinoma.

High Energy Imaging for Therapy Verification (Fenster, Munro) with J.R. Cunningham and A. Rawlinson (Clinical Physics group)

One of the major problems in radiation therapy is ensuring that the correct region of the body receives the x-ray treatment and that the surrounding tissues are spared. Therapy verification checks are used to visualize the regions of the patient exposed to the treatment beam. Film is currently used for therapy localization. However, film suffers from two problems: (1) the images obtained with film have low contrast so that anatomical structures are difficult to visualize; and, (2) use of film is labour intensive, requiring much time and effort to produce the (poor) images. Two methods can be used to improve therapy localization: (1) modifying the treatment machines so that they can produce x-rays of diagnostic energies which are more suited to imaging; or, (2) developing an imaging device which can effectively use the high energy treatment beams to generate images. Modifying treatment machines would be quite difficult and would solve the localization problem for only those treatment machines that had been modified. An imaging device, however, would not only improve therapy localization on all treatment machines, but could be used for other tasks such as checking the x-ray beam being used to treat the patient (quality assurance checks) and checking the computer-dose calculations used to predict the dose distribution within the patient.

A project is underway in collaboration with the radiotherapy group to develop an imaging device which can be used for therapy localization with high energy (6-25 MV) x-ray beams. The project is divided into two separate parts. First, various parameters of high energy x-ray beams will be measured (modulation transfer function, noise power spectrum) to determine the limits in image quality that can be expected when imaging with a therapy x-ray beam. Then using this information, a system will be designed which can be used for therapy localization. Although the design details have not been finalized, the imaging system will probably comprise the following components. The x-ray detector will consist of a tungsten plate which will efficiently interact with the high energy x-ray beams. The x-ray photons that interact will be converted into light photons by a fluorescent screen sitting in close contact with the tungsten plate. The image on the fluorescent screen will be reflected by a 45° mirror and focussed by a large aperture, high-quality lens system onto a vidicon tube capable of slow scan imaging. The lens, vidicon tube and any ancillary electronics will be outside of the primary treatment beam. The image will then be digitized, enhanced using image-processing techniques and displayed on a TV monitor.

■ Anthropomorphic Radiological Phantoms (Yaffe, Caldwell)

The early radiologic diagnosis of disease depends critically on the optimization of image quality. Existing techniques for measuring image quality are useful but often must oversimplify the imaging task, and do not provide a realistic test of the many aspects of image quality. We are developing a novel method for producing radiological test objects which closely simulate the x-ray transmission properties of the human body[11]. The technique involves the extraction of information from actual patient radiographs using digital image-processing methods and the incorporation of such detail into a test object by a combination of mechanical and photographic means. When such phantoms are radiographed they produce images similar to those from patients and facilitate the evaluation by radiologists of subtle differences in image quality.

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Magnetic Resonance Imaging Research

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Magnetic Resonance (MR) Imaging is a new diagnostic modality that has established an important role for itself in neurological imaging. However, it is still an evolving technology with major improvements in image quality, speed of imaging and special purpose techniques becoming available. Also, the role of MR imaging in parts of the body other than the head is still being defined.

MR images differ significantly from X-ray images because the gray scale exhibited depends on multiple parameters which are properties of the tissue being imaged and the characteristics of the MR signals being acquired. In particular, much of the contrast in MR images arises from differences in the relaxation times (T_1 and T_2) of the tissues being imaged. Therefore, optimal usage of MR imaging requires a fundamental knowledge of the biological behaviour of these relaxation parameters and their changes with disease processes.

The magnetic resonance imaging research group has focussed its activities in three areas: i) to understand the relaxation behaviour of tissues and its impact on MR imaging; ii) to improve the imaging process through elimination of artifacts and; iii) to evaluate the role of MR imaging in cancer diagnoses and staging.

Relaxation In Tissues

Since many different types of MR images can be taken, it is necessary to have a knowledge of the properties of the tissues which are to be imaged so that optimal imaging sequences

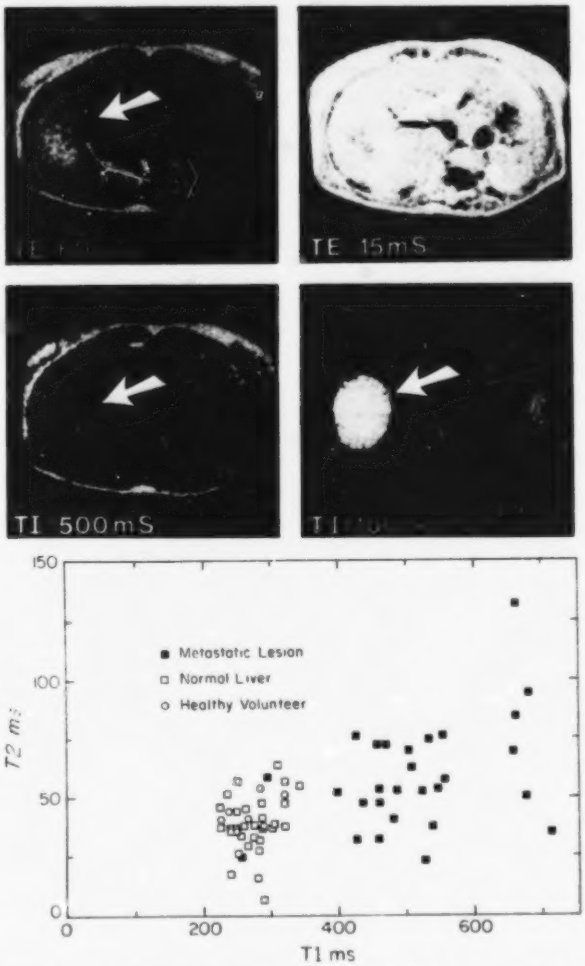


Figure 1. (a) A comparison of different MR imaging acquisitions showing a liver metastasis with varying contrast. (b) The required knowledge of the characteristics of the tissue to allow an optimal choice of the imaging sequence to be determined.

can be selected. Figure 1a shows four different MR images of a patient with a liver metastasis in which the tumor has bright contrast, dark contrast or is indistinguishable from the surrounding liver. To determine which is the best type of imaging, it is necessary to have a knowledge of the distributions of tissue relaxation times as shown in Figure 1b. Based on such knowledge, the pulse sequences optimal for specific clinical evaluations can be developed.

A more detailed look at the relaxation characteristics of normal and malignant tissue reveals that their relaxation times cannot be adequately represented by single numbers. Tissues show continuous distributions of relaxation times which have patterns that are characteristic of the type of tissue and its pathological condition. Methods for measuring these characteristic distributions have been developed in the laboratory and work is underway to determine the biological basis of the distributions that have been obtained.

Improvements In Imaging

Every imaging system produces some low level signals that do not correspond to patient anatomy and which, therefore, obscure the interpretation of the image. These artifacts need to be understood and eliminated from the imaging process. MR imaging presents a unique collection of artifacts which have not been encountered before in medical diagnoses.

An example is the "ghosting" artifact arising from patient breathing shown in Figure 2a. By synchronization of the data acquisition, the ghosts can be deliberately positioned to interfere minimally with the image as in Figure 2b. A better solution is to eliminate the ghosts altogether as in Figure 2c. Efficient methods for eliminating these motion artifacts have been investigated.

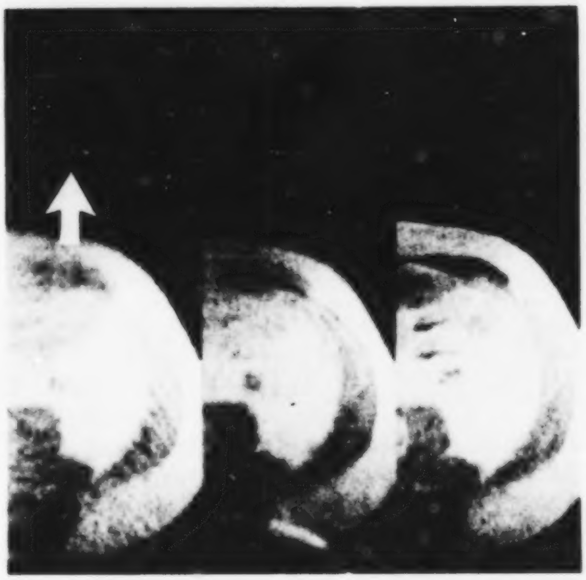


Figure 2. Abdominal images of a breathing patient showing the ghost artifacts arising from motion on the left, a synchronized acquisition to move the ghosts outside of the anatomical image, centre, and a fully corrected image, right.

Other artifacts that have been eliminated are those arising from stimulated echoes in multi-echo decays, from non-uniformities of the receiver coils, from limited sampling of the Fourier space data, and from phase inversion of the complex images.

Evaluation Of MR Imaging For Cancer

It is necessary to determine whether the different images obtained with MR provide unique information for the diagnoses and management of cancer patients. To do this, the MR

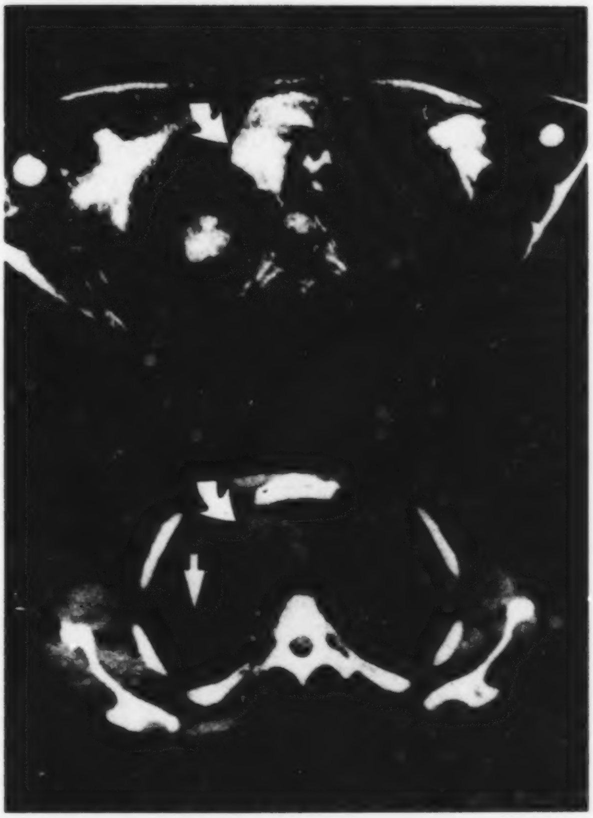
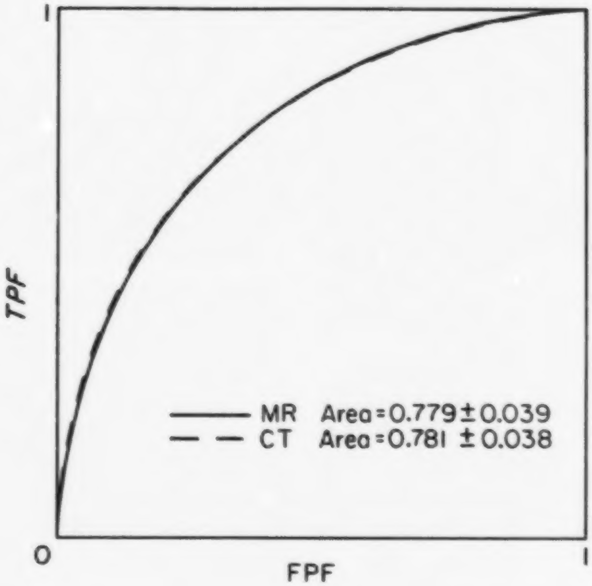


Figure 3. a) and b) show MR and CT images of a patient with lung cancer and a metastatic lesion in the mediastinum (curved arrow). c) shows that MR and CT perform equivalently at this diagnostic task.

images must be compared with conventional images for a large series of patients where the actual state of disease is known by other means. Figures 3a and b show transverse sections through the chest of a patient with lung cancer (straight arrow). The important question for patient management is whether there is secondary disease in the mediastinum. In this case, both MR in 3a and computed tomography (CT) in 3b, showed a mass in the mediastinum which was confirmed surgically. The question is whether in a large series of patients, MR or CT is more accurate at this task. The answer is shown in Figure 3c where the true positive fraction is scored against the false positive fraction for both MR and CT. The results are equivalent and thus MR, at this stage of development, does not show any advantage over CT for this imaging task.

Similar results have also been found for liver metastases leading to a conclusion that, although MR is unparalleled for neurological imaging, it requires further development if it is to play a significant role in oncological body imaging. In particular, more specificity of MR for tumors must be achieved to realize the full potential of MR in cancer.



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Ultrasound Imaging Research Program

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Ultrasonic imaging plays an important role in the detection and management of a wide range of human diseases. The general method by which medical ultrasonic images (B-scans) are produced, closely parallels the system of underwater navigation called "Sonar". An ultrasound transducer is excited with a short voltage pulse, causing the generation of an ultrasound pulse which propagates into the tissue. The frequency used is generally between 1 and 10 MHz and the physical length of the ultrasound pulse is on the order of 1 mm in tissue. The lateral dimension of the beam is controlled by the transducer size and focussing properties. As the ultrasound pulse travels through tissue, echoes representing discontinuities are received by the transducer. The transducer converts the echoes into electrical signals as a function of time and displays them as bright spots on a television monitor. The distances between the bright spots are proportional to the distances between the corresponding structures in the tissue. Each pulse sent out by the transducer results in one line of image information. As the transducer is swept across the tissue, a tomographic image is generated.

Although ultrasound has been used most effectively in obstetrics, abdominal imaging and dynamic imaging of the heart, the advent of new technologies and scanning approaches has opened up a number of promising areas of specialization in diagnostic imaging. Among these techniques, intra-operative ultrasound, peripheral vascular imaging, realtime blood flow mapping, tissue characterization and breast imaging are important examples.

The work of the ultrasound group is divided into three important areas:

1. The development and assessment of new ultrasound transducer technologies.
2. The study of the basic physical interactions of ultrasound with tissue.
3. The development of new ultrasound scanners, particularly in the area of breast imaging.

The objective of this work is to reach a better understanding of the ultrasound imaging process and to exploit this knowledge in the development of new clinical instrumentation for the detection of tumors in the body.

Ultrasound Transducer Technology

Ultrasound transducers are responsible for the vital task of transmitting and receiving ultrasonic energy. The transducer therefore determines both the sensitivity and resolution of an ultrasound scanner. Conventional scanners tend to produce images with pronounced lateral streaking due to their poor lateral resolution (2 to 3 mm). We have developed a novel transducer called the cone/annular array hybrid which provides a lateral resolution of only 0.5 mm over a large imaging depth[1]. Based on this high resolution design, two breast scanners have been developed by the Ultrasound Group and are presently being evaluated at The Princess Margaret Hospital and Women's College Hospital. Realtime hand held probes have emerged as the predominant clinical ultrasound imaging tool. Realtime implies that images are formed at a rate of 10 to 30 frames per second. The production of images at such a fast rate requires severe compromises in the focussing characteristics of the transducer. We are collaborating with Hewlett Packard Laboratories to develop a strongly focussed realtime ultrasound imaging system. The heart of this system is a jointly developed annular array transducer capable of a dynamic "zoom" focus with sub-millimeter resolution.

Ultrasound Interaction With Tissue

A better understanding of the formation of ultrasound images is essential to the development of improved imaging methods and quantitative image analysis techniques. Our effort has focussed on three aspects of this problem:

1. Models of image formation.
2. Studies of the cause and control of image noise (speckle).
3. Quantitative measurements of the ultrasonic properties of tissue *in vitro*.

Two models[2,3] have been developed to predict the resolution, contrast and speckle characteristics of ultrasound systems. These models have allowed us to make the first accurate prediction of image contrast for a simple lesion (cyst)[3]. The use of the models in conjunction with our experimental systems has also demonstrated the existence of a small component of multiple scatter in ultrasound images[4].

Speckle, the predominant form of noise in ultrasound images may be minimized by processing the signals from an ultrasound transducer in a variety of ways. The transducers developed here are particularly well suited to this type of approach by virtue of their size and segmented design. Based on phantom studies and theoretical analysis, a method called PISA processing was found to have the best performance[5]. This method of processing is being implemented in a breast scanner here at the OCI.

Extensive studies of the ultrasonic properties of human tissue are ongoing. The ultrasound "macroscope" has enabled us to make the first quantitative measurements of the ultrasonic backscatter and attenuation coefficients of normal and abnormal breast tissue[6]. This information is of great value for the development of future generation of scanners. Recently, we have developed an ultrasonic microscope system that operates at a frequency of 100 MHz and has a resolution of ~ 15 micrometers (about the size of a single cell). Figure 1 shows the first image obtained with this system. It represents a map of the attenuation coefficient of muscle tissue. The muscle fibers are shown in cross-section at the top of the image and are viewed longitudinally in the lower part of the image. The ultrasonic microscope will be used to study the sources of ultrasound scatter in human tissue and will be tested as a possible tool for the examination of tissue pathology.

Ultrasound Imaging Systems

Two breast imaging systems based on the cone/annular array transducer technology have been completed. The first system has been installed at Women's College Hospital where Dr. Eve Fishell has now examined approximately 1500 patients. This system provides 140 high resolution transverse image planes of the left and right breasts of each patient. The images for each breast are stored on two video disks and are rapidly sequenced for review by the radiologist.

Ultrasound is very successful in detecting and diagnosing benign abnormalities such as liquid-filled cysts and abscesses. In preliminary results, it appears however that ultrasound is less accurate than x-ray mammography in detecting tumors, particularly for patients having fatty breasts. However, these two techniques complement each other since some carcinomas and cysts detected by ultrasound in dense breasts were not observed by x-ray mammography[7].

The data from the Women's College Hospital study is presently being entered into a computerized data base for statistical analysis.

The second breast scanning system is installed at Princess Margaret Hospital. This system incorporates the PISA signal processing method described earlier. The objective is to compare the detectability of lesions with and without the new processing method.

A prototype realtime annular array imaging system is being developed in collaboration with Hewlett Packard Laboratories. This system contains a "multi-channel digital front end" which is critical to the development of future generations of scanners. Delivery of the prototype scanner is expected in the fall of 1986. After an initial clinical evaluation this system will be used to explore new methods of ultrasound imaging, particularly those that exploit the use of phase information to detect blood flow and measure attenuation *in vivo*.

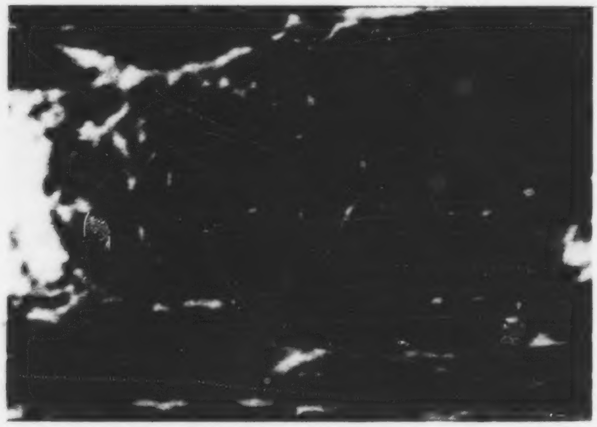

Figure 1. Ultrasound Microscope image obtained at 100 MHz of muscle fibers in longitudinal section (bottom) and transverse section (top). The width of the scan is approximately 1 mm.

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Macromolecular and Cellular Electron Microscopy

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Our research is divided into two separate but interrelated streams. One is the development and modification of electron microscope techniques and instrumentation as required for and applied to biological problems; the other is the determination of the structure of active and inactive chromatin, using our newly developed imaging techniques as tools. In addition, as part of the development process, we have studied the structure of smaller macromolecules or complexes, and developed image analysis approaches which remove virtually all of the subjective bias in the selection of structures in noisy images.

Active and Inactive Chromatin Structure (Ottensmeyer, Yu, Zabal, Rutherford)

Each mammalian cell contains DNA with a total length of about 150 cm. This DNA has to be folded in such a way that it fits into a cell nucleus approximately 0.001 cm small. This compaction is carried out primarily with the help of proteins called histones. However, the final structure, chromatin, is not an inert package of protein and DNA, but a dynamic manifold which variously covers up or exposes specific genes along the DNA molecule as the information is required in the life and function, or malfunction, of a cell or for its differentiation into different organs or tissues.

We are studying the structure of the quiescent form of chromatin starting with its basic subunit, the nucleosome. Using two-dimensional electron energy loss analysis and three-dimensional reconstruction from electron micrographs, we have already determined the 3-D structure of the nucleosome DNA-protein core[1]. The work is being extended to examination of different forms of the nucleosome core and their structural relationship to H1, a protein that assists in further compaction of the DNA, and to HMG proteins, which appear to be indicative of a more active state of chromatin.

To approach the active chromatin structure more directly, a program is underway to extract the functioning genome of the tumor-forming virus SV-40 during its infectious cycle in cultured mammalian cells. This viral DNA uses the cellular protein machinery, mimicking cellular chromatin. Its small size makes it possible to separate its chromatin from cellular chromatin and so offers the possibility of examining the structure of a known, well-defined set of active genes.

Electron Energy Loss Analysis And Image Processing (Andrews, Yu, Farrow, Frankland, Dignam, Ezers)

The approach toward the structure of active and quiescent chromatin above was made possible by our development of an imaging electron energy filter installed in our Siemens 102 electron microscope[2]. This instrument is capable of detecting and identifying as few as 30 atoms at a resolution potential of 3 to 5 nm (billionths of a meter). The applications of the device go far beyond our own interests into metallurgy, solid state physics, semiconductors, corrosion, protein synthesis, muscle metabolism, bone growth etc. As a consequence, we have been able to persuade Zeiss of West Germany to build and market such an electron microscope.

Our own developments are continuing to improve the device in energy resolution and to make its use possible for more easily produced, thicker biological specimens. One aim is the potential use in electron microscope specimens of the chemically specific colours and dyes of light microscopy while at the same time producing images with electron microscopic spatial resolution.

The necessity of computer image processing of the micrographs produced via the imaging electron energy loss filter has taken us into other areas of image processing, such as the development of algorithms for direct 3-D reconstruction from projections at random angles and non-linear approaches for the selection of structures from noisy images[3]. These investigations are being continued and will include approaches such as maximum entropy methods. In addition to speed analysis of micrographs, we have installed a micro-VAX based densitometric TV-computer link.

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Clinical Physics

Radiation Dosimetry

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Research activities in this group are directed to the goal of practical improvement of physical aspects of radiotherapy. This includes endeavors that are concerned with improving accuracy and correlating observed biological effects with radiation dose, and the development of equipment concerned with radiation treatments.

It is generally agreed that the radiation dose delivered in a course of radiation treatments should be within ±5 per cent of the prescription. This is really a very demanding requirement because many different activities are involved. These include basic calibration of measuring instruments, quality control of radiation treatment units, patient dose calculations and the positioning of the patient for treatment. All of these steps are being examined and improved at the OCI.

Instrument Calibrations

The accurate determination of absorbed dose involves measurements with ionization chambers and the application of a number of multiplying factors. We have been cooperating with a number of physicists elsewhere in examining the accuracy of some of these factors and one member of the group, J.R. Cunningham, has been part of a team that recently produced dosimetry protocols for the American Association of Physicists in Medicine (AAPM)[1] and for the International Atomic Energy Agency (IAEA). Much of the data used in these protocols was supplied from The Ontario Cancer Institute. More recently we have investigated one of the factors, the ratio of averaged mass-energy absorption coefficients using Monte Carlo techniques and determined the way it depends on the size of the radiation beam and the depth within an irradiated medium[2].

Charge Effects In Plastic Phantoms

We have found that plastic materials, which are widely used as substitutes for tissue in radiation dosimetry experiments, can, because of their insulating properties, build up sufficient electric charge to cause errors of several percent in dose measurements. This was a new and surprising finding and was first viewed with some considerable skepticism by the international medical physics community. It has now been confirmed and the physics of the effect is being studied further with a view to decreasing or eliminating the effect[3]

Patient Dose Calculation

We are also continuing to assess and develop procedures for calculating dose distributions used in treatment planning. A "pencil beam" approach which has been proposed for use with electron beams, appears to be very powerful and general in scope and is also being developed for photon beam calculations. It has the potential to address the as yet unsolved problem of dealing with tissue inhomogeneities that give rise to a loss of electronic equilibrium. This is a large project and work will continue over several years.

Treatment Machine Development

The improvement of the beam characteristics of high energy x-ray linacs has been of continuing interest to our group. We have been studying the problem of the energy spread across the beam which reportedly causes "horns" on the dose distribution, complicates treatment planning dose calculations and makes uncertain the conversion from dosimeter response to dose. In practice, beam characteristics depend not only on the x-ray spectrum but also on the electron contamination in the beam and we are using a unique experimental approach to sort out these two effects. We have developed a charge detector to measure electron contamination and a special ion chamber ratio method to determine x-ray spectrum changes. The use of these new tools will enable us, we believe, to make further improvements in linac head design. We plan to separately develop the ion chamber ratio method as a practical means to assess the quality of x-ray beams since it provides a quick measure of the average energy. This application however, requires a detailed knowledge of the detector response in mono-energetic photon beams, information which will be obtained experimentally as well as by calculation using Monte Carlo methods.

Dose Calculation For Internal Source

Conventionally, dosage calculations for internal sources assume no correction other than the source geometry. The introduction of remote after loading devices, such as the Calitron (developed at the OCI) and other commercial units, where metal spacers are used to keep radioactive sources in the desired distribution, complicates the dose calculation. The shielding effect of these small spacers must be handled properly in order to obtain the correct isodose distribution. If the attenuation of these spacers alone is used to correct the dose, our results show that it may over-estimate their effect by as much as a factor of two due to the contribution of radiation scattered by the phantom.Our first approach to solving this problem is to divide the dose at any point into two components; primary and scattered radiation, similar to methods used for external radiation therapy. We propose to obtain data for the scattered component from Monte Carlo calculations such that its variation with phantom size could also be accounted for. It is expected that when this work is completed, body inhomogeneities could also be accounted for in this type of dose calculation.

Dose Distribution At Interfaces

The dose to tissue in the vicinity of non-tissue-like material may vary considerably depending on the energy and direction of the x-rays, the contour and atomic number of the materials, and the distance from the interface. Existing information on this subject is incomplete and is principally for primary beam radiation only. We have found, for instance, that the production of low energy scattered photons at large field sizes and tissue depths leads to doses at high atomic number interfaces and is very much larger than previously reported[4,5]. We are repeating previous work using a different experimental technique and will then examine radiotherapy situations such as bone marrow dose for large field irradiation and tissue dose in dental and prosthetic implant regions.

Interpretation Of Ion Chamber Measured Dose Distributions

All patient dose data are derived primarily from ion chamber measurements. Although high credibility is given to data measured under near electronic equilibrium conditions, there is still confusion when results are obtained in regions of high dose gradients in x-ray and electron beams. Historically such data was obtained using extrapolation chambers but calibrated commercial ion chambers cannot have this function. We are experimentally investigating the design parameters of parallel plate ion chambers to

a) minimize the need for extrapolation
b) obtain correction factors for existing chambers.

Safety Systems For Multi-Mode Accelerators

Final verification of the operating mode of radiotherapy accelerators may be performed totally or in part by manufacturer-supplied computer software. Since there is no easy way to check the validity of the software under all operating conditions, we have designed and installed on our newest accelerator, two safety systems which bypass the computer control. The first system monitors the position of the carousel which houses the relevant components for x-ray or electron operation. The second system monitors each pulse of radiation from the machine via a *permanently* installed wire electrode ion chamber installed in the machine head on the patient side of all other relevant components. This system never moves out of the beam path under any condition. In the event of any malfunction which causes the dose during a single pulse to be higher than a preset threshold, all subsequent pulses will be prevented.

Imaging With Radiotherapy Beams

To verify the location of the treatment beam through the patient, images can be taken with film. However, anatomical structures are poorly visualized, if at all, especially for high energy x-rays. To improve the situation, two quite different methods are being explored.

The first method recognizes that image transfer is efficient when a high density plate produces the primary image. To record the image, however, a low noise system must be used since the subject contrast is very low. We have found that the film itself is the dominant source of noise in the image. We are developing a non-film imaging system based on the plate/fluorescent screen/video camera.

The second method recognizes that substantial quantities of diagnostic quality x-rays are generated in bremsstrahlung targets even at high incident electron energies. Normally, these are quickly attenuated in the target and/or flattening filters which are made of high atomic number materials. If a low atomic number target is used with no flattening filter, diagnostic quality images could be produced using standard fluorescent screen/film systems which discriminate between low and high energy x-rays. At present, diagnostic quality images seem possible without further optimization for thin body sections but not for thick sections (20 cm) where attenuation of the low energy relative to the high energy becomes significant.

Dose Distribution Measurement Using Magnetic Resonance Imaging

Ferrous sulphate in acidic aqueous solution, known as the Fricke dosimeter, has been used as a chemical dosimeter for many years. In essence, ferrous ions in the solution are oxidized into ferric ions by radiation induced reactions. The increase in ferric ion concentration is conventionally measured by UV photospectrometry. It has been shown[6] that the change in B valence state to the ferric from ferrous ion also sufficiently alters its magnetic properties sufficiently to use nuclear magnetic resonance to measure the ferric ion concentration. It is possible to incorporate the ferrous sulphate in a rigid matrix, and to use magnetic resonance imaging techniques to measure spatial dose distributions.

In our preliminary studies[7], we have successfully devised a system such that ferrous ions are trapped in gelatin and isodose distributions for various radiation beams have been obtained. Figure (1) shows a typical isodose distribution of a 20 MeV electron beam obtained in this way. With further refinement of the technique, it is hoped that we can use this method to verify our dose calculation method under conditions such as in regions of high dose gradient where other dose measuring techniques are inaccurate.

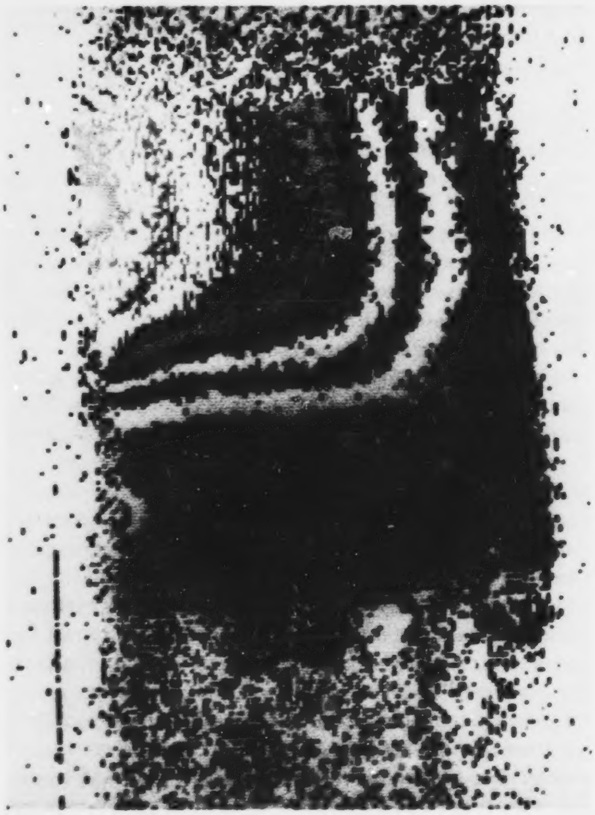

Figure 1.

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Fractionated Radiation Treatment And Radiosensitizers

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Studies With Sensitizers

An important factor affecting the response of tumors to radiation treatment is that they contain radiation-resistant hypoxic cells. Since radiation therapy is usually given as a fractionated course of treatment it is imperative that hypoxic cell radiosensitizers, which are effective in animal tumor systems when used with single doses, also be investigated for their efficacy when given with multiple treatments[1]. Factors such as reoxygenation and the requirement to use smaller sensitizer doses to prevent toxicity during multiple treatments would be expected to reduce the extent of sensitization of hypoxic cells.

Our studies of mouse mammary tumors have concentrated largely on the drug misonidazole and radiation dose fractions of 2 Gy, with the aim of establishing whether, in this tumor system which is capable of extensive reoxygenation, significant sensitization could be obtained. The sensitizer-treated groups did show an improvement in tumor response (growth delay) but only at total doses of 40 Gy or larger. These results suggest that reoxygenation is insufficient to eliminate the influence of hypoxic cells during extended courses of treatment, and support a role for sensitizers in radiotherapy.

Currently available sensitizers are limited, however, by their toxicity in patients; consequently we have been investigating a new drug, RSU-1069, which is claimed to be a much more efficient sensitizer than misonidazole[2]. The studies *in vitro* with CHO and HeLa cells demonstrated that at 37°C the drug was highly toxic to hypoxic cells, but at 4°C (when it was not toxic) it was not a more efficient sensitizer than misonidazole. Our *in vivo* studies[3], using single radiation doses to treat both the KHT Sarcoma and the R1F1 tumor growing in C_3H mice, confirmed that the drug is a highly efficient agent for killing hypoxic cells. Any sensitization of hypoxic cells occurring *in vivo* was masked by the extreme cytotoxicity. Unfortunately, the drug is also very toxic to animals and further studies are required before it can be determined whether the drug has therapeutic potential.

Small Dose Fractions And Hyperfractionation

There is renewed interest in the possibility of improving the therapeutic ratio by modifying fractionation schedules in radiation therapy. The rationale for the use of small (< 2 Gy) dose fractions given multiple times per day (hyperfractionation) is based largely on experimental studies which suggest that the repair capacity of dose-limiting normal tissues which express radiation damage late is greater than that of normal tissues which express their damage early. It is argued that tumors respond similarly to normal tissues which express early damage, and hence a therapeutic gain might be obtained by reducing fraction size and increasing fraction number. There is very little information on the response of tumor (or normal tissues) to dose fractions less than 2 Gy and the arguments are largely based on the extrapolation of results obtained with higher doses in experimental systems.

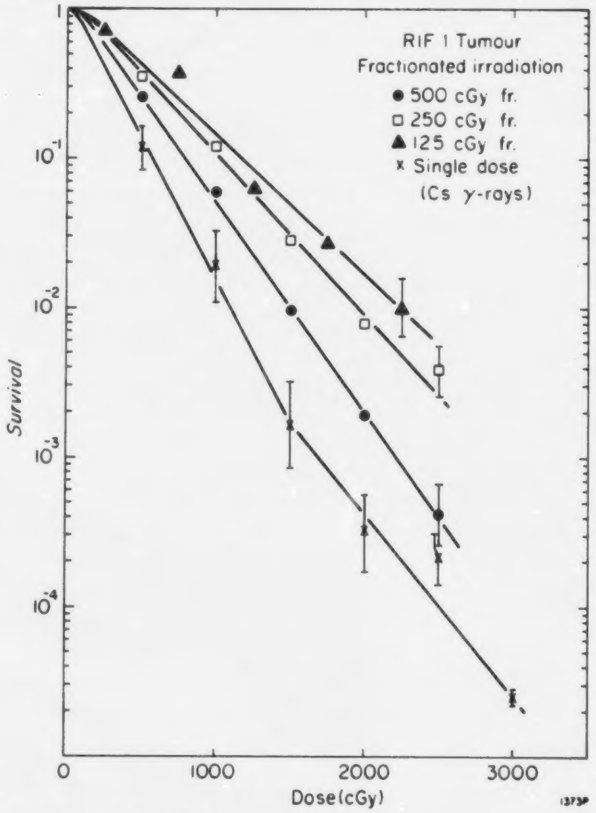

Figure 1. Cell survival curves for RIF-1 tumors, growing intramuscularly in C_3H mice, treated with either a single radiation dose or various different fractionation schedules. The fractionated treatments were given once (500 cGy), twice (250 cGy) or four times (125 cGy) a day with a three-hour interval between fractions.

Consequently we have been studying various fractionation regimes (4 x 1.25 Gy, 2 x 2.5 Gy, 1 x 5 Gy treatments per day) for their efficacy in treating the KHT Sarcoma and the R1F1 tumor. For both, tumor cell survival curves have been derived from *in vitro* plating assays. Initial results for the R1F1 tumor are illustrated in Figure 1 and indicate that the effect of the irradiation decreases with fraction size. The ratio of total doses which give isoeffective survival levels for 1.25 Gy fractions relative to 2.5 Gy fractions appears to be 1.1 - 1.2 for R1F1 tumors. This 10 - 20% increase in dose is similar to the increase in tolerated dose expected for late normal tissue damage when fraction size is reduced from the conventional treatment schedules of 2 - 2.5 Gy to about 1.2 Gy. It is important to obtain further information at higher doses and for other tumors because if this result is confirmed it will suggest no therapeutic gain for hyperfractionation in radiotherapy.

For comparison with the studies of tumor response we have also been examining the response of the normal mouse leg to fractionated radiation treatment. Early acute skin reactions and late leg contraction[4] are being assessed in mice treated with dose schedules similar to those used in the tumor studies. A large single "top-up" dose is being given one day after the fractionated treatments. The size of the "top-up" dose required to achieve a certain level of damage gives a measure of the relative efficacy of the fractionated regimes studied. Initial results suggest that there is relatively little difference in late leg contraction caused by the three different fractionation schedules being studied (4 x 1.25 Gy/day, 2 x 2.5 Gy/day and 1 x 1.5 Gy/day — see Figure 2). These studies are being continued to extend the fractionation schedules to larger total doses.

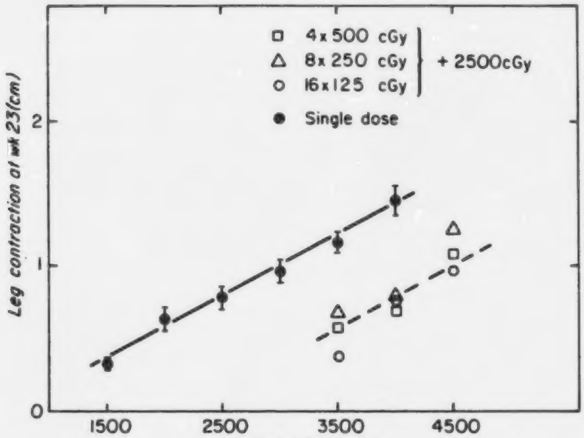

Figure 2. Leg contraction measured in C_3H mice at 23 weeks after different fractionated treatments followed one day later by a single "top-up" dose. The fractionated treatments were given as in Figure 1.

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Tumor Oxygenation And Blood Flow

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The influence of hypoxic cells on the response of tumors to radiation therapy can theoretically be eliminated either by reducing the oxygen concentration in the surrounding normal tissue so that all the cells in the irradiation field are equally resistant or by directly sensitizing the hypoxic cells with increased oxygenation. We are investigating both of these possibilities. The former approach has been tried clinically with tumors of extremities, when a tourniquet was applied and oxygen tension allowed to decline due to metabolism. There was some degree of success in tumor control but also many serious normal tissue complications[1]. Possible explanations for the results are that the small number of large dose fractions used would be expected to give more late damage than conventional treatment or that the normal tissue did not become fully hypoxic. Both of these problems might be overcome by infusing a blood substitute (a deoxygenated Dextran-Hb) which binds oxygen very tightly (P_{50} ~2-5 mm Hg)[2]. Because the blood substitute perfuses all the capillaries, the oxygen tension should be reduced in a rapid uniform manner to give complete hypoxia. Normal fractionation schedules can be used with daily infusion of Dx-Hb through an indwelling catheter, which should help to reduce late damage. Since reoxygenation is not a factor in such treatments it may be appropriate to use an accelerated fractionation schedule to reduce any possible effect of repopulation. Initial studies using pig skin and mouse bone marrow cells have demonstrated that substantial protection can be achieved using this approach.

Blood flow is responsible for the delivery of oxygen and hence might be expected to be a major determinant of the extent of hypoxia in tumors. However we previously demonstrated no correlation between intrinsic blood flow and radiation response in the KHT Sarcoma, implying that an equilibrium is established in the tumors between available oxygen, the hypoxic fraction and cell death. This is consistent with our more recent studies which indicate that acute alterations in blood flow do result in changes in radiation response. A number of anaesthetics and vasoactive agents were found to reduce blood flow in a predictable manner and these reductions correlated with a decreased radiation response consistent with an increase in tumor hypoxia.

However reducing hypoxia by increasing tumor blood flow is likely to be more useful therapeutically. The drug flunarizine, which is a calcium channel blocker active on smooth muscle, has been shown to increase tumor blood flow in rat mammary tumors[3]. Our studies with the drug also indicate an increase in blood flow in the KHT Sarcoma (by 20 to 30%). This increase in flow has been found to correlate with an increase in cell killing (by a factor of 5 to 8) when the tumors were irradiated with a dose of 20 Gy given 15 minutes after drug treatment of the host animal (see Figure 1). This result is consistent with an increase in blood flow causing a reduction in the hypoxic fraction and is currently under further detailed study.

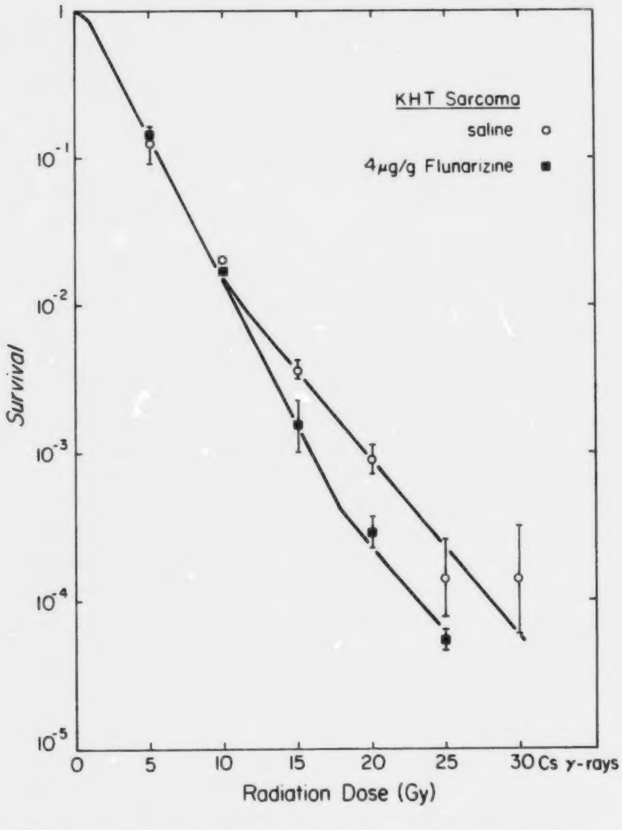

Figure 1. KHT Sarcomas were irradiated starting 15 minutes after the animals had been injected with Flunarizine or saline. Cell survival is plotted as a function of radiation dose. There was very little toxicity when Flunarizine alone was given at doses up to 16 mg/kg. The survival curves suggest that the Flunarizine treatment reduced the fraction of hypoxic cells in the tumors by a factor of about four.

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Effects of Radiation Absorbed Dose on Lung Tissue

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Optimization in radiotherapy requires a detailed understanding of both the actual dose delivered to specific tissues and the radiation response of these tissues to this delivered dose. In general, dose delivery is much better understood than tissue response. Ideally, calculation models should incorporate the effects of biological response so that parameters such as total dose, numbers of fractions, total time and volume can be included in a therapy plan. Until the present time, there has been insufficient clinical data to incorporate adequately such parameters, but our recent studies of the dose-response of lung tissue indicate that this is now an achievable goal.

The implementation of computerized tomography (CT) in radiotherapy planning has allowed us to derive accurate doses for lung irradiation and to obtain dose-response data for pulmonary tissues for single fraction, total lung irradiation procedures[1,2]. Our present half body and total body irradiation prescriptions have been adjusted on the basis of these data. It has also been recognized that the change in lung densities as observed on CT images following lung irradiation can be used as a measure of radiation-induced pulmonary damage both in mice[3] and man[4,5]. A prospective clinical study of 54 patients given partial lung irradiation with fractionated doses has recently been analyzed[5] to yield the dose-response data illustrated in Figure 1. The fractionated schedules were converted to biological estimated single dose values using the equivalent dose (ED) formulation of Wara et al[6].

$$ED = D\,N^{-.377}T^{-.058}$$

This formulation was derived from experiments on the response of mouse lung to fractionated treatment and verified to some extent by these authors in a retrospective analysis of human data. Currently this represents the best time-dose formula available to compare different fractionation schedules leading to the acute phase of pulmonary damage. As more data are accumulated by our clinical studies, we should be able to evaluate this model in more detail and test other possible radiobiological models as they are developed.

At the present time, clinical studies are in progress to assess the relationship between early lung damage (up to six months) and late damage (greater than 6 months) and to assess the effects of chemotherapy on the dose response relationship for both acute and late damage. Again lung density assessed on CT scans is being used as the endpoint for defining pulmonary damage. Even in a large institution such as The Princess Margaret Hospital, one of the main problems of these clinical studies is the patient accrual rate and the time required to obtain sufficient and meaningful data. The longer the follow-up required the more difficult it is to keep patients in the study. It would therefore be desirable to have a measurement endpoint which can identify lung damage early and be a predictor of eventual outcome. Such clinical measurements must essentially be non-evasive and readily acceptable by the patients.

To this end, a study is underway to compare different imaging modalities — especially CT and magnetic resonance imaging (MRI) — to determine whether MRI can provide an earlier measure of lung damage and be predictive of later damage. This comparison will be carried out initially in rats. For MRI, special small animal imaging coils are being designed to provide optimal images for assessing lung damage. Since human dose-response data have already been derived using CT, the eventual results of the animal experiments can be compared directly to the human situation. CT and MRI can then be intercompared directly for the animal experiments to derive an optimum procedure. The final conclusions can be applied in further clinical studies analogous to our present CT studies, to derive dose-response data as expediently as possible for new fractionation schemes (such as hyperfractionation) and new forms of combined modality treatments.

Incorporating Radiobiological Models Into Treatment Planning Programs

A second component of this research program is to incorporate various radiobiological models into our treatment planning programs such that computed isodose plots can be converted to include dose and fractionation effects. As an initial step our computed isodose values within lung tissues can be adjusted by using the ED formulation discussed above and our measured incidence of pulmonary damage (Figure 1).

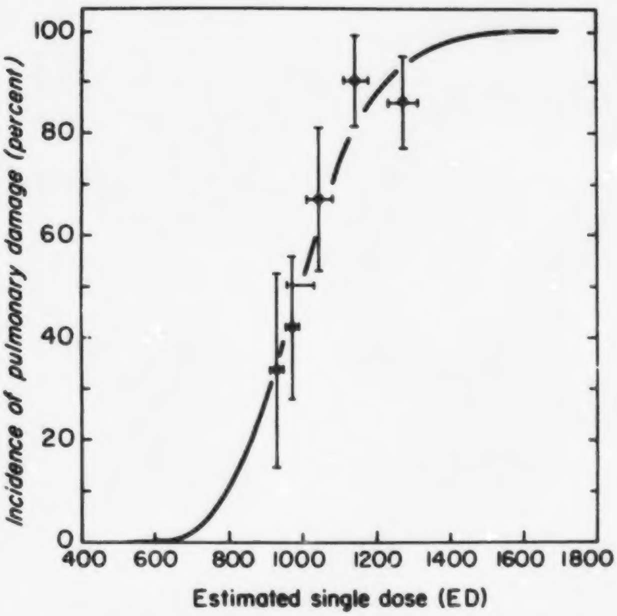


Figure 1. Dose-response data for partial lung, fractionated radiation therapy. ED is described in the text. Data are based on 54 patients.

Figure 2 shows a comparison between a single field, cobalt-60 isodose distribution and the corresponding isoresponse calculation for the dose and fractionation scheme specified. Although this is a hypothetical example, it does illustrate that biological response distributions vary much more rapidly than isodose distributions. Figure 3 is a more realistic

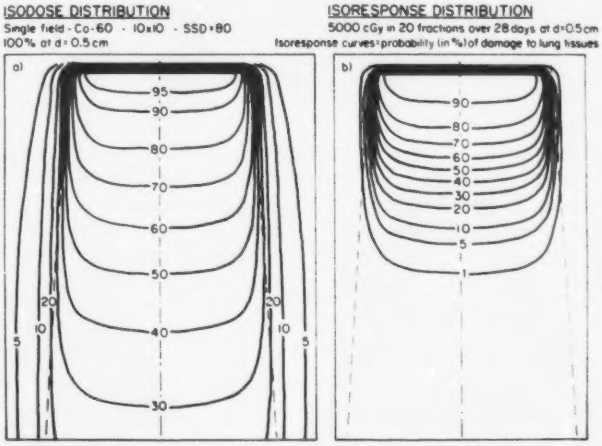
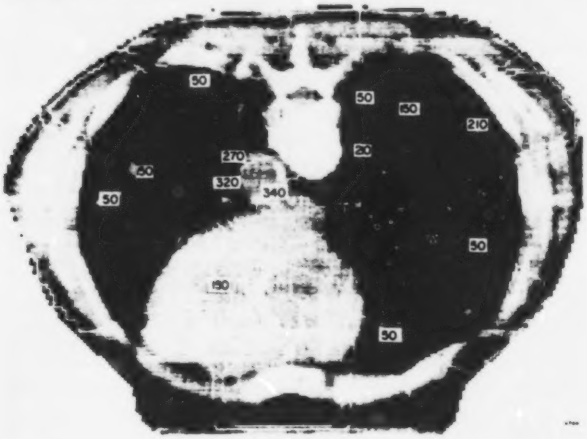

ISODOSE DISTRIBUTION
Single field - Co-60 - 10x10 - SSD=80
100% at d=0.5cm
a)
95
90
80
70
60
50
40
30
20
10
5
ISORESPONSE DISTRIBUTION
5000 cGy in 20 fractions over 28 days at d=0.5cm
Isoresponse curves=probability (in %) of damage to lung tissues
b)
90
80
70
60
50
40
30
20
10
5
1

Figure 2. a) Isodose distribution for a single, 10 x 10 cm^2 cobalt-60 field with a source-to-surface distance of 80 cm. b) Isoresponse distribution indicating probability (in %) of lung damage if 5000 cGy were given in 20 fractions over 28 days at a depth of 0.5 cm.

ISODOSE DISTRIBUTION
6 MV X-rays - 3 field technique
Corrected for inhomogeneities



ISORESPONSE DISTRIBUTION
6 MV X-rays · 3 field technique · 5000 cGy given in
20 fractions over 28 days to 320 % isodose line

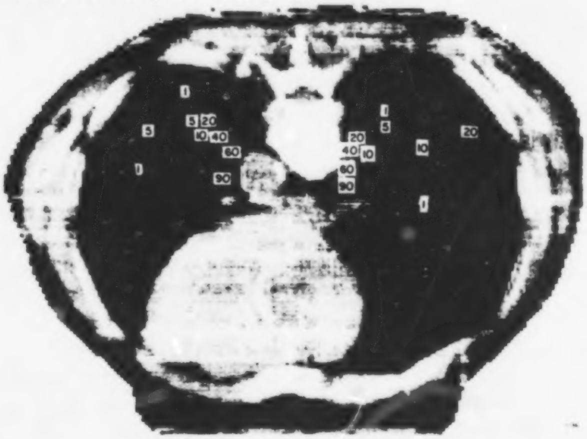


Figure 3. a) Isodose distribution superimposed on a CT image. Three 6 MV x-ray fields are used to treat cancer of the oesophagus. This dose distribution includes corrections for inhomogeneities based on the density data provided by CT. b) Isoresponse distribution for the treatment illustrated in (a) assuming 5000 cGy are given in 20 fractions over 28 days to the 320% line shown in (a).

example where a three field, 6 MV x-ray technique is used for the treatment of cancer of the oesophagus. The upper figure shows an isodose distribution superimposed on a CT image and is corrected for low density lung tissues while the lower figure shows the corresponding isoresponse distribution for the dose and fractionation scheme specified.

It is recognized that the implementation of radiobiological models in treatment planning programs is in a stage of infancy compared to absorbed dose calculation schemes. However, the detailed derivation of dose-response data as described above will allow for an optimization of radiotherapeutic practice as well as the testing of clinically relevant radiobiological models.

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Lectures and Papers

■ **Alison RE.** Treatment of Cancer. Fibrocystic disease of the breast and breast cancer. Peterborough In-County Health Unit In-Service Program on Cancer. Peterborough, Ontario, April, 1985.

■ **Alison RE.** Modalities of cancer education. The message and the media. Invitational Conference on Family Medicine. Athens, Greece, May, 1985.

■ **Alison RE.** Physician's view on self-help groups and health care. Second-Year University of Toronto Medical Students. Toronto, Ontario, March, 1986.

■ **Archer MC.** Biological activity of nitrosomethylbenzylamine in rat liver. International Conference on Organic and Biological Chemistry of Carcinogenic and Carcinostatic Agents Containing Nitrogen-Nitrogen Bonds. Harpers Ferry, West Virginia, May, 1985.

■ **Archer MC (With KC Silinskas and PF Zucker).** Methylation of rat liver DNA by nitrosamines and its relationship to initiation of preneoplastic foci. 76th Annual Meeting of the American Association for Cancer Research. Houston, Texas, May, 1985.

■ **Archer MC.** Mechanisms in nitrosamine carcinogenesis. 3rd International Symposium on Biological Reactive Intermediates. College Park, Maryland, June, 1985.

■ **Archer MC.** Mechanism of organ specificity in nitrosamine carcinogenesis. Southern Ontario Carcinogenesis Group Meeting. Toronto, Ontario, November, 1985.

■ **Aye M (With B Lim, C Izaguirre, C Richardson, MD Minden and HA Messner).** Characterization of reticulofibroblastoid colonies (CFU-RF) derived from bone marrow and long term culture adherent layers. The Canadian Cooperative Group for Bone Marrow Transplantation and Sandoz Canada Inc., Bone Marrow Transplant Symposium, Hotel Sheraton Centre. Toronto, Ontario, October, 1985.

■ **Benchimol S.** Expression of the p53 oncogene in human leukemia. Mount Sinai Hospital Research Institute. Toronto, Ontario, January, 1986.

■ **Bergeron C.** The Canadian Brain Tissue Bank: A resource for Canadian neuroscientists. 8th Annual Meeting of the Canadian College of Neuropsychopharmacology. London, Ontario, May, 1985.

■ **Bergeron C.** Neuropathological diagnosis of Alzheimer's disease. 8th Annual Meeting of the Canadian College of Neuropsychopharmacology. London, Ontario, May, 1985.

■ **Bergsagel DE.** Plasma cell myeloma: Prognostic factors and treatment. Grand Rounds, Montefiore School of Medicine, University of Pittsburgh. Pittsburgh, Pennsylvania, May, 1985.

■ **Bergsagel DE.** Plasma cell neoplasms. Harvard Review Course in Medical Oncology, Harvard Medical School. Boston, Massachusetts, September, 1985.

■ **Bergsagel DE.** Treatment of plasma cell myeloma. Multiple Myeloma Seminar, Faculty of Medicine. Clermont-Ferrand, France, September, 1985.

■ **Bergsagel DE.** The management of Hodgkin's disease without a policy of staging laparotomy. Puerto Rican Society of Hematology, University of Peurto Rico. San Juan, Puerto Rico, February, 1986.

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■ **Bergsagel DE.** Progress in chronic leukemias. Puerto Rican Society of Hematology, University of Puerto Rico. San Juan, Puerto Rico, February, 1986.

■ **Bergasgel DE.** Treatment of plasma cell myeloma. Dr. Jenaro Haddock Memorial Lecture. Puerto Rican Society of Hematology, University of Puerto Rico. San Juan, Puerto Rico, February, 1986.

■ **Blend R.** Alternate methods of breast imaging. Joint symposium on breast imaging. Annual Meeting of The Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Blend R (With PY Poon, RG Perrin, H Dunlap, M Bronskill and M Henkleman).** MRI in spinal cord compression. Annual Meeting of The Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Blend R (With GM Thomas, BE Black and B Tudor Roberts).** Real time sonography in cancer of the cervix. Annual Meeting of The Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Blend R.** Transrectal ultrasonography. Symposium on urologic ultrasound. Invited speaker and panelist, Wellesley Hospital. Toronto, Ontario, November, 1985.

■ **Blend R.** Trans-rectal ultrasound of prostate and seminal vesicles. Society of Diagnostic Medical Sonographers at Toronto Institute of Medical Technology. Toronto, Ontario, April, 1986.

■ **Boyd NF.** Approaches to studying the prevention of breast cancer. Grand Rounds, Department of Family and Community Medicine, Wellesley Hospital. Toronto, Ontario, April, 1985.

■ **Boyd NF.** Approaches to studying the prevention of breast cancer. Annual Meeting of the Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Boyd NF (With W Webber).** A critique of the methodology used by studies investigating breast cancer in benign breast disease. Annual Meeting, Royal College of Physicians and Surgeons of Canada. Vancouver, British Columbia, September, 1985.

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■ **Bronskill MJ.** Current Developments in the use of NMR imaging in medicine. Canadian Association of Physicists 1985 Congress. Fredricton, New Brunswick, June, 1985.

■ **Buick RN.** EGFR gene abnormalities in human breast cancer. Ludwig Institute for Cancer Research. Bern, Switzerland, April, 1985.

■ **Buick RN.** EGFR gene abnormalities in human breast cancer. Institute for Cancer Research. Lausanne, Switzerland, April, 1985.

■ **Buick RN.** Molecular studies of EGF-mediated growth control in breast cancer cells. Christie Hospital and Holt Radium Institute. Manchester, England, June, 1985.

■ **Buick RN.** EGFR gene

amplification in breast cancer cells. M.D. Anderson Hospital and Tumor Institute. Houston, Texas, September, 1985.

■ **Buick RN.** Stem cell concepts in neoplasia, with particular reference to ovarian carcinoma. National Institute of Environment Safety & Health, (NIESH). Research Triangle Park, North Carolina, October, 1985.

■ **Buick RN.** The stem cell concept as applied to neoplasia. Sloan Kettering Institute. New York, New York, November, 1985.

■ **Buick RN.** Biological and Clinical Implications of the stem cell concept in human malignancy. H. Lee Moffit Symposium on Cancer Biology and Therapeutics. Tampa, Florida, January, 1986.

■ **Buick RN.** Stem cell differentiation in human tumors. Smith Kline and French Lecture Series on Tumor Cell Differentiation, University of Michigan. Ann Arbor, Michigan, January, 1986.

■ **Buick RN.** Oncogenes and gynecologic malignancies. Minisymposium, Society for Gynecologic Investigation. Toronto, Ontario, March, 1986.

■ **Bush RS.** i) The classification of patients with advanced ovarian cancer. ii) Patterns of failure of patients with cancer of the cervix. International Meeting of Gynecological Oncology. Venice-Lido, Italy, April, 1985.

■ **Bush RS.** Multimodality treatment of gynecological cancer. 3rd European Conference on Clinical Oncology. Stockholm, Sweden, June, 1985.

■ **Bush RS.** Cancer of the ovary: surgery, radiation and chemotherapy. Elis Berven Lecture, Swedish Medical Association. Stockholm, Sweden, November, 1985.

■ **Bush RS.** i) Surgery, radiation & chemotherapy in the treatment of patients with carcinoma of the ovary. ii) The place of radiotherapy in the treatment of carcinoma of the ovary. iii) The value of para-aortic radiation for patients with carcinoma of the cervix. iv) Influence of prognostic factors on choice of therapy in patients with malignant lymphoma. Midwinter Oncology Conference, Los Angeles Radiological Society. Los Angeles, California, January-February, 1986.

■ **Bush RS.** i) Primary radiotherapy for breast cancer, PMH experience. ii) Breast cancer. iii) Carcinoma of the ovary. iv) Prognostic factors influencing the use of laparotomy in Hodgkin's Disease. v) Prognostic factors influencing the choice of radiation therapy for Non-Hodgkin's lymphoma. vi) Workshop: Lymphoma. vii) Late complications of cancer therapy. viii) Workshop: Complications of cancer therapy. Midwinter Oncology Conference, Post Conference Seminar. Maui, Hawaii, February, 1986.

■ **Bush RS.** Radiation therapy for patients with cancer of the ovary. Indian Society of Oncology. Bombay, India, February, 1986.

■ **Cardinal HN (With A Fenster).** Theoretical optimization of a split xenon ionization detector for dual-energy radiography. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Cillo C (with Hill RP).** Drug resistance and metastases. Lake Ontario Metastasis Group Meeting. Hamilton, Ontario, October, 1985.

■ **Cillo C (With V Ling and R Hill).** Gene amplification and metastasis. UCLA Symposium on Cellular and Molecular Biology of Tumors and Potential Clinical Applications. Springboat Springs, Colorado, January, 1986.

■ **Clark RM.** Current attitudes to the conservative treatment of breast cancer. Ottawa Section of Ontario Association of Medical Radiation Technologists, Annual Education Day. Ottawa, Ontario, April, 1985.

■ **Clark RM.** A different viewpoint: Results of limited breast removal for cancer. Wellesley Hospital, Department of Family Medicine Symposium on Breast Disease. Toronto, Ontario, April, 1985.

■ **Clark RM.** Breast Cancer: Care vs cure. The Challenge to High Tech Treatment: The Conservative Treatment of Breast Cancer with Radiotherapy. London Regional Cancer Centre and St. Joseph's Hospital Oncology Unit. London, Ontario, May, 1985.

■ **Clark RM.** The stage I Ontario Clinical Oncology Group Study. Toronto Breast Group, Academy of Medicine, Toronto, Ontario, May, 1985.

■ **Clark RM.** Television faces cancer. Canadian Cancer Society's National Campaign Conference. Toronto, Ontario, October, 1985.

■ **Clark RM.** Conservative management of breast cancer. The Institute for Social Workers in Oncology. Ontario Cancer Institute. Toronto, Ontario, October, 1985.

■ **Clark RM.** Breast cancer — dispelling the myths. Dalhousie University. Halifax, Nova Scotia, October, 1985.

■ **Clark RM.** Breast cancer 1985 — time for change. The Margaret and Norman Gosse Lecture. Dalhousie University. Halifax, Nova Scotia, October, 1985.

■ **Cummings BJ.** Delayed morbidity from radiation therapy in children treated for head and neck neoplasms. 5th Joint Meeting of the American Society and Head and Neck Surgery and the Society of Head and Neck Surgeons. Dorado Beach, Puerto Rico, May, 1985.

■ **Cummings BJ.** The conservative treatment of rectal cancer by radiation therapy. Plenary Session: Rectal Cancer. 16th International Congress of Radiology. Honolulu, Hawaii, July, 1985.

■ **Cummings BJ.** Does the addition of chemotherapy to radiation therapy improve the therapeutic ratio for anal canal carcinoma? 16th International Congress of Radiology. Honolulu, Hawaii, July, 1985.

■ **Cummings BJ.** Radiotherapy for carcinoma of the rectum. Mid-West Colon and Rectal Society. Toronto, Ontario, September, 1985.

■ **Cummings BJ.** Radiation treatment of the regional lymph nodes in carcinoma of the anal canal. 27th Annual Meeting of the American Society of Therapeutic Radiology and Oncology. Miami, Florida, October, 1985.

■ **Cummings BJ.** The role of radiation therapy for vascular tumors of the head and neck. American Academy of Otolaryngology Head and Neck Surgery. Atlanta, Georgia, October, 1985.

■ **Cummings, BJ.** The role of radiation therapy in the treatment of anal carcinoma. Thomas Jefferson University. Philadelphia, Pennsylvania, November, 1985.

■ **Cummings BJ.** Review of adjuvant radiation therapy for rectal cancer. Conference: Rectocolon Cancer, State of the Art. Daytona Beach, Florida, February, 1986.

■ **Cummings BJ.** The role of

radiation and chemotherapy in the treatment of anal carcinoma, The Princess Margaret Hospital experience in treating juvenile angiofibromas, The role of adjuvant radiation therapy for rectal carcinoma. Department of Radiation Therapy. Gainesville, Florida, February, 1986.

- **Cunningham IA (With BB Hobbs and A Fenster).** A new system for quantitative arterial imaging and blood flow measurements. 11th Canadian Medical and Biological Engineering Conference. Kingston, Ontario, May, 1985.
- **Cunningham IA (With BB Hobbs and A Fenster).** A new system for quantitative arterial imaging and blood flow measurements. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.
- **Cunningham JR.** Calculation algorithms used in computers. Teaching course on radiation physics for clinical radiotherapy. European Society for Therapeutic Radiology and Oncology. Louven, Belgium, September, 1985.
- **Cunningham JR.** The dose planning system. What input data is needed? Teaching course on Radiation Physics For Clinical Radiotherapy. European Society for Therapeutic Radiology and Oncology. Louven, Belgium, September, 1985.
- **Cunningham JR.** High energy beam calibration for radiotherapy. Radiological Society of North America. Chicago, Illinois, November, 1985.
- **Cunningham JR.** Computers in 3-dimensional treatment planning. Invited speaker, University of Wisconsin. Madison, Wisconsin, March, 1986.
- **Curtis JE (With W Hill, D Tritchler, A Bird, MD Minden and HA Messner).** Development of a computerized data collection and record system. The Canadian Cooperative Group for Bone Marrow Transplantation and Sandoz Canada Inc. Bone Marrow Transplant Symposium, Hotel Sheraton Centre. Toronto, Ontario, October, 1985.
- **D'Astous FT (With FS Foster, PC Johns, MJ Yaffe, DW Brown and MJ Bronskill).** Ultrasound, x-ray and magnetic resonance breast tissue characterization. 4th Meeting of the World Federation for Ultrasound in Medicine and Biology. Sydney, Australia, July, 1985.
- **Deachman MJ.** Psychological responses accompanying the diagnosis and treatment of cancer. Canada AM Interview. Toronto, Ontario, July, 1985.
- **Deachman MJ.** Psychological responses accompanying diagnosis and treatment for cancer. The Betty Kennedy Radio Show. Interview. Toronto, Ontario, July 1985.
- **Deachman MJ (With M Silberfeld).** An introduction to the psychological medicine service at The Princess Margaret Hospital. Orientation Programme of Psychiatric Residents and Interns, Wellesley Hospital. Toronto, Ontario, July, 1985.
- **Deachman MJ.** Psycho-Social issues and interventions with patients and their families. Workshop on Physical Assessment for Registered Nurses, George Brown College. Toronto, Ontario, October, 1985.
- **Deachman MJ.** Psycho-Social issues and interventions with patients and their families. Ontario Occupational Health Nurses. Toronto, Ontario, November, 1985.
- **Deachman MJ.** Sex-role stereotyping in the clinical judgement of health states. Annual Meeting of the Group-Without-A-Name (PSYCHIATRY). Toronto, Ontario, November, 1985.
- **Dembo AJ.** Carcinoma of ovary. Department of Obstetrics/Gynecology and Department of Therapeutic Radiology, Henry Ford Hospital. Detroit, Michigan, April, 1985.
- **Dembo AJ.** Carcinoma of the ovary — Update and current management. 21st Annual Cancer Symposium, Victoria Hospital. London, Ontario, April, 1985.
- **Dembo AJ.** Prognostic factors for recurrence in the postmenopausal breast cancer (Tamoxifen vs. control). Academy of Medicine, Oncology Section. Toronto, Ontario, May, 1985.
- **Dembo AJ.** i) Role of adjuvant radiation therapy in endometrical cancer. ii) Irradiation in ovarian cancer. Gynecological Cancer Symposium, Swedish Hospital Medical Center. Seattle, Washington, May, 1985.
- **Dembo AJ.** Abdominopelvic radiotherapy in ovarian cancer — Princess Margaret Hospital data. Antoni van Leeuwenhoek Hospital. Amsterdam, The Netherlands, June, 1985.
- **Dembo AJ.** Clinicopathological correlates in ovarian cancer. Therapeutic Implications. Vrije Universiteit. Amsterdam, The Netherlands, June, 1985.
- **Dembo AJ.** i) Extended field radiation in cervical cancer. ii) Radiation therapy in epithelial cancer of the ovary. Boorhaave Course, Leeuwenhorst Congress Centre. Noordwijkerhout, The Netherlands, June, 1985.
- **Dembo AJ.** i) Radiotherapy of lymph nodal metastases in gynecologic malignancies. ii) Radiotherapy of patients with metastatic nodes, ca. ovary. International Meeting of Gynecological Oncology: Lymphatic Metastases in Gynecological Malignant Tumors. Rome, Italy, September, 1985.
- **Dembo AJ.** The management of carcinoma of the ovary — Prognostic factors and selection of therapy. Washington University School of Medicine, Mallinckrodt Institute of Radiology, St. Luke's Hospital. St. Louis, Missouri, October, 1985.
- **Dembo AJ.** Refresher course on ovarian cancer. American Society for Therapeutic Radiology and Oncology. Miami Beach, Florida, October, 1985.
- **Dembo AJ.** Radiation therapy — Ovarian Cancer. Cincinnati Cancer Conference IV. Cincinnati, Ohio, November, 1985.
- **Dembo AJ.** Whole abdominal radiation in ovarian cancer. Mid-Atlantic Oncology Program Meeting. Baltimore, Maryland, November, 1985.
- **Dembo AJ.** Radiation therapy in epithelial ovarian cancer. Diagnosis and Treatment Strategies for Gynecologic Cancer. 29th Annual Clinical Conference. The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute. Houston, Texas, November, 1985.
- **Dembo AJ.** Rationale of current strategies. Ovarian Cancer Symposium: Therapeutic Results and Exciting New Leads. New York University Medical Center. New York, New York, December, 1985.
- **Dembo AJ.** i) Role of radiation therapy in stages I and II carcinoma of the endometrium. ii) The role of external beam radiation in ovarian cancer. Cowan Cancer Symposium. Salt Lake City, Utah, January, 1986.

■ **Dembo AJ.** Prognostic factors in stage I epithelial ovarian carcinoma. Society of Gynecologic Oncologists. 17th Annual Meeting. Palm Springs, California, February, 1986.

■ **Dembo AJ.** Extended-field radiotherapy in cervical cancer. Refresher Course, Society of Gynecologic Oncologists. 17th Annual Meeting. Palm Springs, California, February, 1986.

■ **Dembo AJ.** i) Radiotherapy of endometrical cancer. ii) Radiotherapy of ovarian cancer. University of California, Irvine — First International Cancer Conference. Irvine, California, February, 1986.

■ **Ege GN.** Lymphoscintigraphy. American College of Nuclear Medicine Annual Meeting. New York, New York, October, 1985.

■ **Enge V (With S Fenwick).** Developing self learning materials. Health Care Staff Educators Association of Ontario. Toronto, Ontario, May, 1985.

■ **Enge V.** Bone marrow transplantation. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.

■ **Enge V (With S Fenwick).** The Hickman catheter experience — A strategy for care. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.

■ **Feld R.** The role of the surgeon in lung cancer trials. Visiting Professor, Montreal General Hospital. Montreal, Quebec, April, 1985.

■ **Feld R.** Small cell lung cancer. The Sir Mortimer B. Davis Jewish General Hospital. Montreal, Quebec, April, 1985.

■ **Feld R.** Management of the febrile neutropenic patient with cancer. The Sir Mortimer B. Davis Jewish General Hospital. Montreal, Quebec, April, 1985.

■ **Feld R.** Canadian multicentre randomized trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell carcinoma of the lung. American Society of Clinical Oncology Meeting. Houston, Texas, May, 1985.

■ **Feld R.** Canadian multicentre randomized trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell carcinoma of the lung. 14th International Congress of Chemotherapy. Kyoto, Japan, June, 1985.

■ **Feld R.** Canadian small cell lung cancer studies. Tokyo Cancer Hospital. Tokyo, Japan, June, 1985.

■ **Feld R.** Late complications of therapy of lung cancer. IV World Conference on Lung Cancer. Toronto, Ontario, August, 1985.

■ **Feld R.** Canadian multicenter randomized trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell carcinoma of the lung (BR.3). IV World Conference on Lung Cancer. Toronto, Ontario, August, 1985.

■ **Feld R.** Canadian multicenter randomized trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell carcinoma of the lung (BR.3). Royal College of Physicians and Surgeons Annual Meeting. Vancouver, British Columbia, September, 1985.

■ **Feld R.** Infections in the comprised host. Family Practitioners and Internists. Barrie, Ontario, September, 1985.

■ **Feld R.** Infections in the immunologically comprised host. Hoffman-La Roche Limited, Clinical Research Department. Toronto, Ontario, October, 1985.

■ **Feld R.** CEA: A useful prognostic marker for small cell lung cancer. Inter-American Society for Chemotherapy Annual Meeting. Tampa, Florida, December, 1985.

■ **Feld R.** Chemotherapy for small cell lung cancer. Inter-American Society for Chemotherapy Annual Meeting. Tampa, Florida, December, 1985.

■ **Feld R.** An evaluation of third generation cephalosporins — formulary considerations. Canadian Society of Hospital Pharmacists, Central Ontario Branch. Toronto, Ontario, January, 1986.

■ **Feld R.** Third generation cephalosporins. St. Joseph's General Hospital, Department of Family Practice. North Bay, Ontario, January, 1986.

■ **Fenster A.** A xenon detector array for scanned projection radiography. Upstate New York Chapter of the American Association for Physicists in Medicine. Rochester, New York, April, 1985.

■ **Fenster A.** A photo-diode array imaging system for angiography and blood flow measurements. Association for the Advancement of Medical Instrumentation. Boston, Massachusetts, May, 1985.

■ **Fenwick S (With V Enge).** Developing self-learning materials. Health Care Staff Educators' Association of Ontario. Toronto, Ontario, May, 1985.

■ **Fenwick S (With V Enge).** The Hickman catheter experience — A strategy for care. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.

■ **Fitzpatrick PJ.** Acute epithelioma — an aggressive form of squamous cell carcinoma. American Radium Society. Acapulco, Mexico, April, 1985.

■ **Fitzpatrick PJ.** Carcinoma of the lip. Canadian Association of Radiologists. Toronto, Ontario, May, 1985.

■ **Fitzpatrick PJ.** Treatment of squamous cell carcinoma of the eyelids. Canadian Association of Radiologists. Toronto, Ontario, May, 1985.

■ **Fitzpatrick PJ.** Cancer of the head and neck. Princess Margaret Hospital experience. 4th Annual Cancer Update. Manitoulin-Sudbury Oncology Symposium. Sudbury, Ontario, October, 1985.

■ **Fitzpatrick PJ.** Panel Chairman General Session. 4th Annual Cancer Update. Manitoulin-Sudbury Oncology Symposium. Sudbury, Ontario, October, 1985.

■ **Fitzpatrick PJ.** Salivary gland tumors. American Society of Therapeutic Radiologists. Miami, Florida, October, 1985.

■ **Fitzpatrick PJ.** Tumors of the skin and their treatment by radiotherapy. University of Cincinnati and American Cancer Society. Cincinnati, Ohio, October, 1985.

■ **Fitzpatrick PJ.** Acute epithelioma or keratoacanthoma. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Fitzpatrick PJ.** Salivary gland tumors. Eastern Great Lakes Head and Neck Oncology Society. Buffalo, New York, November, 1985.

■ **Fitzpatrick PJ.** Acute epithelioma. Visiting Professor, Memorial Sloan Kettering Hospital. New York, New York, January, 1986.

- **Fitzpatrick PJ.** Magnafield irradiation in humans and dogs. Visiting Professor, Memorial Sloan Kettering Hospital. New York, New York, January, 1986.
- **Fitzpatrick PJ.** Metastatic cancer in the neck from an unknown primary tumor. Visiting professor, Memorial Sloan Kettering Hospital. New York, New York. January, 1986.
- **Fitzpatrick PJ.** Multiple primary tumors in the upper digestive tract. Visiting Professor, Memorial Sloan Kettering Hospital. New York, New York, January, 1986.
- **Fitzpatrick PJ.** Choroidal melanoma and its treatment by radiotherapy (plaques and external beam). Combined Ocular Melanoma Study Group. Dallas, Texas, February, 1986.
- **Fornasier VL.** Osteoarthritis and the subchondral cyst. Canadian Congress of Laboratory Medicine. Edmonton, Alberta, June, 1985.
- **Fornasier VL.** Pathogenesis of osteo-arthritis. The Annual Conference of the Chinese Medical Association of the Republic of China. Taipei, Taiwan, July, 1985.
- **Fornasier VL.** Parosteal lipoma — A review. International Skeletal Society, Closed Meeting. Edinburgh, Scotland, October, 1985.
- **Fornasier, VL.** Arthrosis, arthritis, arthroplasty and revision. Visiting lecturer to the Chinese University of Hong Kong at the Prince of Wales Hospital. Hong Kong, November, 1985.
- **Fornasier VL.** Long course on bone and joint diseases. Visiting Professor, Sun Yat Sen University of Medical Sciences. Canton, China, November, 1985.
- **Fornasier, VL.** Pathology and pathogenesis of avascular neorosis. AO ASIF Hip Course, Sunnybrook Medical Centre. Toronto, Ontario, January, 1986.
- **Foster FS (With EK Fishell, M Khodai, K Harasiewicz and JW Hunt).** Initial clinical performance of a prototype breast imaging system using a conical annular array hybrid transducer. 4th International Congress on the Ultrasonic Examination of the Breast. Sydney, Australia, July, 1985.
- **Galbraith DM.** Detector to measure average energy of bremsstrahlung. 27th Annual Meeting of the American Association of Physicists in Medicine. Seattle, Washington, August, 1985.
- **Gospodarowicz MK.** Definitive radiation in the management of bladder cancer. Montreal General Hospital. Montreal, Quebec, October, 1985.
- **Gospodarowicz MK.** The role of xrt in the management of localized lymphomas. Royal Victoria Hospital. Montreal, Quebec, October, 1985.
- **Grant J.** Technical and experimental considerations of electron arc therapy. Ontario Cancer Treatment and Research Foundation Conference. London, Ontario, April, 1985.
- **Greenberg C.** Helping people help themselves through nutrition. Institute for Social Workers in Oncology. Toronto, Ontario, October, 1985.
- **Greenberg C.** Oncology nutrition care model. Nova Scotia Dietetic Association Fall Conference 1985. Wolfville, Nova Scotia, October, 1985.
- **Goettler D.** Nutrition and cancer therapy. University of Toronto nutrition students. Toronto, Ontario, March, 1986.
- **Hasselback R.** Cancer quackery. Current topics in primary practice. Sunnybrook Medical Centre. Toronto, Ontario, April, 1985.
- **Hasselback R.** New developments in causation and prevention of cancer. Canadian Cancer Society Metro Toronto District. Etobicoke, Ontario, April, 1985.
- **Hasselback R.** Breast disease. Women of Seneca College, Seneca College. North York, Ontario, May, 1985.
- **Hasselback R.** Questions and answers regarding cancer. Workplace Education Services. Ontario Division, Canadian Cancer Society. Toronto, Ontario, May, 1985.
- **Hasselback R.** Cancer Research. Royal Bank Canadian Cancer Society Volunteer Canvassers. The Princess Margaret Hospital Lodge. Toronto, Ontario, September, 1985.
- **Hasselback R.** New developments in causation and prevention of cancer. Oakville Unit, Canadian Cancer Society. Oakville, Ontario, September, 1985.
- **Hasselback R.** An overview of cancer. The Institute for Social Workers in Oncology. Toronto, Ontario, October, 1985.
- **Hasselback R.** New advances in cancer research. East York Unit, Canadian Cancer Society. Toronto, Ontario, October, 1985.
- **Hasselback R.** Recent developments in diagnosis and chemotherapy of cancer. Ontario Occupational Health Nurses Association Annual Conference. Toronto Convention Centre. Toronto, Ontario, November, 1985.
- **Hasselback R.** Unconventional remedies. Symptom Control in Patients with Cancer. Sunnybrook Medical Centre. Toronto, Ontario, February, 1986.
- **Henkelman RM.** The importance and the problems of evaluating a new diagnostic modality: Experience with MRI in oncology. St. Joseph's Hospital Research Day. London, Ontario, May, 1985.
- **Henkelman RM.** Developments in cancer diagnosis. Canadian Cancer Society. Toronto, Ontario, October, 1985.
- **Henkelman RM.** Medical imaging: Physics opens a new window into the human body. Canadian Undergraduate Physics Conference. Winnipeg, Manitoba, October, 1985.
- **Henkelman RM.** NMR in oncology. Manitoba Cancer Foundation. Winnipeg, Manitoba, October, 1985.
- **Henkelman RM.** Investigating the role of MRI in oncology. B.C. Cancer Control Agency. Vancouver, British Columbia, January, 1986.
- **Henkelman RM.** Imaging and cancer. Canadian Cancer Society, Manitoba Division. Winnipeg, Manitoba, February, 1986.
- **Henkelman RM.** MR imaging: Basic principles. Radiology Ground Rounds, University of Toronto. Toronto, Ontario, February, 1986.
- **Henkelman RM.** Imaging and cancer. Canadian Cancer Society Board Meeting. Toronto, Ontario, March, 1986.
- **Herman S.** Magnetic resonance imaging of soft tissue tumors of the extremities. Annual Meeting of the Canadian Association of Radiologists. Toronto, Ontario, June, 1985.
- **Hill RP.** Dynamic heterogeneity and metastasis. Lake Ontario Metastasis Group Meeting. Buffalo, New York, April, 1985.
- **Hill RP.** Superfractionated irradiation of

tumors. 33rd Annual Meeting, Radiation Research Society. Los Angeles, California, May, 1985.

- **Hill RP.** Sensitizers and radiation dose fractionation: Results and interpretations. Combined Modalities Meeting. Clearwater, Florida, October, 1985.
- **Hunt JW.** Review of deep heating using ultrasonic beams. 33rd Annual Meeting, Radiation Research Society. Los Angeles, California, May, 1985.
- **Hunt JW (With AT Kerr, MS Patterson and FS Foster).** Improved ultrasound images using conical hybrid transducers. Frontiers of Engineering and Computing in Health Care, IEEE Engineering in Medicine and Biology Society, 7th Annual Conference. Chicago, Illinois, September, 1985.
- **Hyland RH (With CK Chan, MA Hutcheon, HA Messner, MD Minden, JE Curtis, SJ Urbanski, JP Sculier, M Alexander, MS Rodriquez and G Fyles).** Bronchiolitis in allogeneic bone marrow transplant recipients. The Canadian Cooperative Group for Bone Marrow Transplantation and Sandoz Canada Inc. Bone Marrow Transplant Symposium, Hotel Sheraton Centre. Toronto, Ontario, October, 1985.
- **Innes AC (With HN Cardinal, BB Hobbs and A Fenster).** A beam hardening correction for digital angiography. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.
- **Irvine DM (With BE Brown, DL Crooks, JG Roberts, R Browne and HB Porter).** Psychosocial adjustment in women with breast cancer. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.
- **Japp B.** Three-dimensional treatment planning with electrons. TP-11 User's Group. 27th Annual Meeting of the American Association of Physicists in Medicine. Seattle, Washington, August, 1985.
- **Japp B.** Eye plaque users group. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.
- **Kerr AT (With MS Patterson, FS Foster and JW Hunt).** Speckle reduction in pulse-echo images by using phase insensitive summation and multiplicative techniques. 14th International Symposium on Acoustical Imaging. The Hague, The Netherlands, April, 1985.
- **Kerr AT (With MS Patterson, FS Foster and JW Hunt).** Image speckle reduction for large aperture transducers using phase-insensitive addition and multiplicative techniques. Symposium on Computers in Ultrasound, Drexel University. Philadelphia, Pennsylvania, September, 1985.
- **Ling V.** Evidence for multidrug resistance in human cancers. Cancer and Leukemia Group B National Meeting. Boston, Massachusetts, April, 1985.
- **Ling V.** Genetic analysis of multidrug resistance. Memorial Sloan Kettering Cancer Center. New York, New York, April, 1985.
- **Ling V.** Genetic analysis of multidrug resistance. Center for Genetics, The University of Illinois, College of Medicine at Chicago. Chicago, Illinois, April, 1985.
- **Ling V.** Genetics and clinical implications of multidrug resistance in cancer chemotherapy. Department of Cell Biology, M.D. Anderson Hospital and Tumor Institute. The University of Texas System Cancer Center. Houston, Texas, April, 1985.
- **Ling V.** Genetics of pleiotropic multidrug resistance. Dana-Farber Cancer Institute, Harvard Medical School. Boston, Massachusetts, April, 1985.
- **Ling V.** Multidrug resistance and chemotherapy. Department of Pediatric Molecular Biology Lecture Series. University of Western Ontario. London, Ontario, April, 1985.
- **Ling V.** Resistance to cancer chemotherapy. Symposium on Cancer Technology Assessment. Merck, Sharp and Dohme. Branchburg Farm, New Jersey, April, 1985.
- **Ling V.** Multidrug resistance. The Netherland Cancer Institute. Amsterdam, The Netherlands, May, 1985.
- **Ling V.** Multidrug resistance and membrane alterations in cancer cell. Second International Conference on Progress in Cancer Research. San Remo, Italy, May, 1985.
- **Ling V.** Resistance in cancer chemotherapy. Scuola Superiore di Oncologia e Scienze. Santa Margherita, Italy, May, 1985.
- **Ling V.** Multidrug resistance in cell cultures. Drug Resistance Workshop, 14th International Congress of Chemotherapy. Kyoto, Japan, June, 1985.
- **Ling V (With JH Gerlach and DR Bell).** P-glycoprotein over-expression in animal and human cancers. 28th Annual Meeting, Canadian Federation of Biological Society. Toronto, Ontario, June, 1985.
- **Ling V.** Drug resistance. FASEB Summer Research Conference. Saxton's River, Vermont, July, 1985.
- **Ling V.** Amplification of the P-glycoprotein genes. International Symposium on the Genetics of Development. Honey Harbour, Ontario, September, 1985.
- **Ling V.** Expression of multidrug resistance in cancer cells. Symposium on Drug Resistance. Annual Scientific Meeting, The Royal College of Physicians and Surgeons of Canada. Vancouver, British Columbia, September, 1985.
- **Ling V.** Mechanisms of drug resistance and their potential reversal. Special Lecture — Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.
- **Ling V.** Clinical implication of drug resistance. Plenary Session, Annual Scientific Meeting of the Clinical Oncology Society of Australia. Sydney, Australia, November, 1985.
- **Ling V.** The genetics of multidrug resistance. The Cancer Institute, Peter MacCallum Hospital. Melbourne, Australia, November, 1985.
- **Ling V.** Molecular biology of multidrug resistance. Symposium on Drug Resistance, Annual Scientific Meeting of the Clinical Oncology Society of Australia. Sydney, Australia, November, 1985.
- **Ling V.** Multidrug resistance and over-expression of P-glycoprotein in tumor cells. Workshop on Cellular Biology of Pleiotropic Drug Resistance. National Institutes of Health, National Cancer Institute, Division of Cancer Treatment. Bethesda, Maryland, December, 1985.
- **Ling V.** Multidrug resistance: Implications for cancer chemotherapy. Symposium on Drug Resistance. 27th Annual Meeting American Society for Hematology. New Orleans, Louisiana, December, 1985.
- **Ling V.** Pleiotropic drug resistance. Symposium on Antitumor Drug Resistance.

Annual Meeting of the Biochemical Society. London, England, December, 1985.

■ **Ling V.** Drug resistance and chemotherapy. Regional Hematology Rounds, Hamilton General Hospital. Hamilton, Ontario, January, 1986.

■ **Ling V.** P-glycoprotein and multidrug resistance. Abbott-UCLA Symposium on Cellular and Molecular Biology of Tumors and Potential Clinical Applications. Steamboat Springs, Colorado, January, 1986.

■ **Ling V.** P-glycoprotein in multidrug resistant cells. The Cleveland Clinic Foundation. Cleveland, Ohio, March, 1986.

■ **Llewellyn-Thomas HA.** Patients and spouses: Methodologic issues in the measurement of value differences. 10th National Nursing Research Conference. Toronto, Ontario, April, 1985.

■ **Lockwood G.** Deep heating using focussed, scanning ultrasound beams. Canadian Association of Radiologists, 48th Annual Meeting. Toronto, Ontario, June, 1985.

■ **McParland BJ.** A status report on an empirical approach to a pencil-beam algorithm for electron treatment planning. Ottawa Civic Hospital. Ottawa, Ontario, January, 1986.

■ **McParland BJ.** A status report on an empirical approach to a pencil-beam algorithm for electron treatment planning. Montreal General Hospital. Montreal, Quebec, March, 1986.

■ **McParland BJ.** Treatment planning for electron beams: The pencil-beam approach. Cancer Treatment and Research Foundation of Nova Scotia. Halifax, Nova Scotia, March, 1986.

■ **Mah K (With J Van Dyk, T Keane and PY Poon).** Acute radiation-induced lung damage: A prospective clinical study following fractionated radiation therapy. 4th World Conference on Lung Cancer. Toronto, Ontario, August, 1985.

■ **Mah K (With J Van Dyk, T Keane and PY Poon).** Acute radiation-induced pulmonary damage: Dose response to fractionated radiation therapy. 27th Annual Meeting of the American Society of Therapeutic Radiology and Oncology. Miami, Florida, October, 1985.

■ **Mah K (With PY Poon, J Van Dyk, T Keane, IF Majewsky and DF Rideout).** CT findings in acute radiation-induced pulmonary damage. 71st Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Mak TW.** T cell antigen receptors. Conference on T Cell Receptor. Pasadena, California, April, 1985.

■ **Mak TW.** T cell antigen receptors. EMBO Workshop on T Cell Receptors. Marseilles, France, April, 1985.

■ **Mak TW.** T cell antigen receptors. International Congress of Differentation. Heidelberg, West Germany, April, 1985.

■ **Mak TW.** T cell antigen receptors. Department of Microbiology, University of Geneva. Geneva, Switzerland, May, 1985.

■ **Mak TW.** T cell antigen receptors. Max Planck Institute. Freiberg, West Germany, May, 1985.

■ **Mak TW.** T cell antigen receptors. International Symposium on Mediators of Immune Regulation and Immunotherapy. London, Ontario, June, 1985.

■ **Mak TW.** Genes encoding the T cell antigen receptors. 1985 FASEB Meeting on Lymphocytes and Antigens. Saxton's River, Vermont, July, 1985.

■ **Mak TW.** Genes encoding the T cell antigen receptors. 1985 FASEB Meeting on Somatic Cell Genetics. Saxton's River, Vermont, July, 1985.

■ **Mak TW.** T cell antigen receptors. International Workshop on Transplantation. Montebello, Quebec, July, 1985.

■ **Mak TW.** T cell receptors. First Military Medical University. Beijing, China, August, 1985. Mak TW. T cell receptors. Symposium on Cancer. Perspective for Control. Beijing, China, August, 1985.

■ **Mak TW.** Clincal applications of T cell receptor genes. Yale University School of Medicine. New Haven, Connecticut, September, 1985.

■ **Mak TW.** T cell antigen receptors. Cancer Institute. Tokyo, Japan, September, 1985.

■ **Mak TW.** T cell antigen receptors. Japanese Biochemical Society Annual Meeting. Sindai, Japan, September, 1985.

■ **Mak TW.** T cell antigen receptors. Kyoto University. Kyoto, Japan, September, 1985.

■ **Mak TW.** T cell antigen receptors. Kyushu University. Fukuoka City, Japan, September, 1985.

■ **Mak TW.** T cell antigen receptors. Osaka University. Osaka, Japan, September, 1985.

■ **Mak TW.** T cell antigen receptors. Tokyo University. Tokyo, Japan, September, 1985

■ **Mak TW.** T cell antigen receptors. University of British Columbia. Vancouver, British Columbia, September, 1985.

■ **Mak TW.** T cell antigen receptors. University of Connecticut Medical Center. Farmington, Connecticut, September, 1985.

■ **Mak TW.** T cell antigen receptors. Yale University. New Haven, Connecticut, September, 1985.

■ **Mak TW.** T cell antigen receptors. Emory University. Atlanta, Georgia, October, 1985.

■ **Mak TW.** T cell antigen receptors. Stanford University. Stanford, California, October, 1985.

■ **Mak TW.** T cell antigen receptors. Symposium on Autoimmunity. San Francisco, California, October, 1985.

■ **Mak TW.** T cell antigen receptors. University of California. San Francisco, California, October, 1985.

■ **Mak TW.** T cell antigen receptors. University of Michigan. Ann Arbor, Michigan, October, 1985.

■ **Mak TW.** T cell antigen receptors. University of Philadelphia, School of Medicine. Philadelphia, Pennsylvania, October, 1985.

■ **Mak TW.** T cell antigen receptors. British Society for Immunology Meeting on Recognition of Immunogenes by Antibodies and T Cells. London, England, November, 1985.

■ **Mak TW.** T cell antigen receptors. Institut fur Genetik der Universitat zu Koln. Koln, West Germany, November, 1985.

■ **Mak TW.** T cell antigen receptors. McGill University. Montreal, Quebec, November, 1985.

■ **Mak TW.** T cell antigen receptors. Symposium on Minimal Residual Diseases. Rotterdam, The Netherlands, November, 1985.

■ **Mak TW.** T cell antigen receptors. University of

Rochester. Rochester, New York, November, 1985.

■ **Mak TW.** T cell antigen receptors. French Society of Immunology Annual Meeting. Paris, France, December, 1985.

■ **Mak TW.** T cell antigen receptors. Presidential Symposium of the American Society of Hematology. Louisianna, New Orleans, December, 1985.

■ **Mak TW.** T cell antigen receptors. Royal Free Hospital. London, England, December, 1985.

■ **Mak TW.** T cell antigen receptors. University of Louisianna. Louisianna, New Orleans, December, 1985.

■ **Mak TW.** T cell antigen receptors. UCLA Symposium on B Cell T Cell Receptors. Lake Tahoe, California, January, 1986.

■ **Mak TW.** T cell antigen receptors. American Leukemia Society Annual Meeting. Tampa, Florida, March, 1986.

■ **Martell E (With WB Taylor).** A matrix dosimeter to measure linear accelerator beam uniformity and calibration. Poster Session, Canadian Medical and Biological Engineering. Kingston, Ontario, May, 1985.

■ **Messner HA.** Immunodepression and the immunocomprised host with immunopotentiation. Annual Meeting of the Canadian Association of Critical Care Nurses. Toronto, Ontario, September, 1985.

■ **Messner HA.** Pluripotent stem cells: Bone Marrow transplantation, hemopoietic malignancies. Guest Lecturer, Jiangxi Institute of Medical Sciences. Nanchang, China, October, 1985.

■ **Messner HA (With G Fyles, JE Curtis, MD Minden, D Tritchler and G Lockwood).** The use of cyclosporin A in the treatment of acute GVHD. The Canadian Cooperative Group for Bone Marrow Transplantation and Sandoz Canada Inc. Bone Marrow Transplant Symposium. Toronto, Ontario, October, 1985.

■ **Messner HA.** Cell culture of hemopoiesis, T cells, B cells and bone marrow transplantation. Immunology Conference, Mount Sinai Hospital. Toronto, Ontario, January, 1986.

■ **Messner HA.** Human clonogenic hemopoietic precursors in cell culture. Technological Innovations in Laboratory Hematology. Banff, Alberta, March, 1986.

■ **Miller RG.** Role of veto cell in immunoregulation. International Symposium. Mediators of Immune Regulation and Immunology. London, Ontario, June, 1985.

■ **Miller RG.** T cell recognition phenomenon. Canadian Federation of Biological Societies Toronto Symposium on T cell receptor. Toronto, Ontario, June, 1985.

■ **Miller RG.** Veto cells and self/non-self discrimination. 7th Lake Ontario Immunology Conference. Saranac Lake, New York, June, 1985.

■ **Miller RG.** The peculiar nature of recognition by T cells. Departments of Pathology and Molecular Biology, Case Western University. Cleveland, Ohio, October, 1985.

■ **Miller RG.** Rapid changes in specificty within single clones of cytolytic effector cells. Departments of Pathology and Molecular Biology, Case Western University. Cleveland, Ohio, October, 1985.

■ **Miller RG.** Veto cells. Canadian Conference on Bone Marrow Transplantation. Toronto, Ontario, October, 1985.

■ **Miller RG.** In vitro development and regulation of the T cell specificy repertoire. Memorial Sloan Kettering Cancer Center. New York, New York, January, 1986.

■ **Miller RG.** T cell differentiation. UCLA Symposium on Molecular and Cellular Biology. T and B Cell Repertoire Development. Lake Tahoe, California, January, 1986.

■ **Minden MD.** T cell receptor and gene rearrangement. Hematology Grand Rounds, Toronto Bayview Regional Cancer Center. Toronto, Ontario, April, 1985.

■ **Minden MD.** Immunoglobulin and T cell receptor antigen structure in leukemias and lymphomas. Grand Rounds and Research Seminar to the Department of Medicine at the University of Ottawa. Ottawa, Ontario, June, 1985.

■ **Minden MD.** The A.B.C.'s of gene probes. Toronto General Hospital, University Area Oncology Rounds. Toronto, Ontario, September, 1985.

■ **Minden MD.** Marrow development and hematopoiesis. Toronto Institute of Medical Technology. Toronto, Ontario, October, 1985.

■ **Minden MD.** Normal marrow-marrow development and hematopoiesis. Toronto Institute of Medical Technology. Toronto, Ontario, October, 1985.

■ **Minden MD.** Studies of T-receptor gene rearrangement. Great Lakes Oncology Group. Albany, New York, October, 1985.

■ **Minden MD (With JE Curtis and HA Messner).** Origin of leukemic relapse after bone marrow transplantation detected by restriction fragment length polymorphism. The Canadian Cooperative Group for Bone Marrow Transplantation and Sandoz Canada Inc. Bone Marrow Transplant Symposium, Hotel Sheraton Centre. Toronto, Ontario, October, 1985.

■ **Minden MD.** The use of molecular probes to characterize hemopoietic malignancies. Dade Seminar. The Role of Recombinant DNA Technology in Hematology, Inn on the Park. Toronto, Ontario, October, 1985.

■ **Minkin S.** On optimal designs for binary data. Queen's University. Kingston, Ontario, May, 1985.

■ **Minkin S.** On optimal designs for binary data. Annual Meeting, Canadian Statistical Society. Winnipeg, Manitoba, June, 1985.

■ **Minden S.** Likelihood-based confidence regions for log-linear models. 20th Joint National Meeting, Operations Research Society of America and the Institute of Management Sciences. Atlanta, Georgia, November, 1985.

■ **Miyamoto N.** Characterization of a transcription factor recognizing the adenovirus-2 major late promoter. Ontario Cell & Virus Group, McMaster University. Hamilton, Ontario, November, 1985.

■ **Munro PN (With JA Rawlinson and A Fenster).** Imaging characteristics of x-ray detectors used for radiotherapy localization. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Nagai MJ.** Safe handling of chemotherapy. Hamilton Regional Outreach Program. Hamilton, Ontario, October, 1985.

■ **Ottensmeyer FP.** Electron energy loss analysis and imaging in biology. American Association of Microbiology Symposium on New Method in Electron Microscopy. Las Vegas, Nevada, April, 1985.

■ **Ottensmeyer FP.** Electron spectroscopic imaging and the 3D computer reconstruction of the nucleosome. Engineering Science Symposium on the Physical Theory in Biology, Physics Department, University of Toronto. Toronto, Ontario, May, 1985.

■ **Ottensmeyer FP.** Microanalysis of cartilage and chromatin by new high resolution energy analysis. Special Lecture, American Association of Anatomists. Toronto, Ontario, May, 1985.

■ **Ottensmeyer FP.** Electron spectroscopic imaging: Structure and microanalysis of cartilage and chromatin. Department of Anatomy, University of Calgary. Calgary, Alberta, June, 1985.

■ **Ottensmeyer FP.** Dissecting EELS: Chemical microanalysis of chromatin and cartilage. Academy of Medicine, Pathology Division. Toronto, Ontario, September, 1985.

■ **Ottensmeyer FP.** Imaging in cancer research and cancer diagnosis. Public Information Conference, Canadian Cancer Society. Orillia, Ontario, September, 1985.

■ **Ottensmeyer FP.** Electron spectroscopic imaging: Thin-specimen microanalysis from chromatin to metal alloys. Atomic Energy of Canada Limited. Pinawa, Manitoba, November, 1985.

■ **Ottensmeyer FP.** Microanalysis and structure determination of chromatin and cartilage. Department of Biology, University of Manitoba. Winnipeg, Manitoba, November, 1985.

■ **Ottensmeyer FP.** The high resolution structure and chemical analysis of cartilage and chromatin by electron spectroscopic imaging, a new technique for microanalysis. Montreal Physiological Society. Montreal, Quebec, February, 1986.

■ **Pakalniskis A.** Osteoporosis and vitamins. Catholic Women's League Meeting. Toronto, Ontario, October, 1985.

■ **Panthaki L.** Collaborative approach to staff support: The process of developing a formal programme. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.

■ **Payne P.** Evaluation: A step to success in patient education. 3rd National Symposium in Oncology Nursing. Edmonton, Alberta, September, 1985.

■ **Payne P.** The validation process: A vehicle for implementing change. Canadian Association Quality Assurance Professionals. Toronto, Ontario, October, 1985.

■ **Payne P.** Cancer patient education: Lecture for overview of cancer nursing. Ryerson Polytechnical Institute. Toronto, Ontario, March, 1986.

■ **Phillips RA.** New approaches to the study of myeloid and lymphoid stem cells. International Symposium on Immunoregulation. London, Ontario, June, 1985.

■ **Phillips RA.** Relative importance of recessive mutation in retinoblastoma. Symposium on the Relative Importance of Point Mutations and Chromosomal Rearrangements. Canadian Congress of Biology. London, Ontario, June, 1985.

■ **Phillips RA.** Expression of new genes introduced into hematopoietic cells with retrovirus vectors. Workshop on Mechanism of B-Cell Neoplasia. National Institutes of Health. Bethesda, Maryland, March, 1986.

■ **Poon PY (With MJ Bronskill, RM Henkelman, DF Rideout, H Shulman, MI Steinhardt, GL Weisbrod and H Dunlap).** Magnetic resonance imaging in the detection of mediastinal lymph nodes metastases in bronchogenic carcinoma. American Roentgen Ray Society 85th Annual Meeting. Boston, Massachusetts, April, 1985.

■ **Poon PY.** Magnetic resonance imaging in oncology. Magnetic Resonance Imaging Symposium. University of Manitoba Health Science Centre. Winnipeg, Manitoba, May, 1985.

■ **Poon PY (With MJ Bronskill, RM Henkelman, HJ Dunlap, DF Rideout, H Shulman, MI Steinhardt, GL Weisbrod, RJ Ginsberg and GA Patterson).** Magnetic resonance imaging in detection of mediastinal involvement in bronchgenic carcinoma. Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Poon PY (With RW McCallum, RM Henkelman, MJ Bronskill, H Dunlap, SB Sutcliffe and M Gospodarowicz).** Magnetic resonance imaging in the detection of extraglandular spread of carcinoma of prostate. Canadian Association of Radiologists. Toronto, Ontario, June, 1985.

■ **Poon PY (With MJ Bronskill, RM Henkelman, HJ Dunlap, DF Rideout, H Shulman, MI Steinhardt, GL Weisbrod, RJ Ginsberg and JD Cooper).** Magnetic resonance imaging in detection of mediastinal involvement in bronchogenic carcinoma. 4th World Conference on Lung Cancer. Toronto, Ontario, August, 1985.

■ **Poon PY (With RM Henkelman, MJ Bronskill, H Dunlap, DF Rideout, H Shulman, MI Steinhardt, GL Weisbrod and RJ Ginsberg).** Magnetic resonance imaging and computed tomography in the detection of mediastinal involvement in bronchogenic carcinoma. Society of Magnetic Resonance in Medicine. London, England, August, 1985.

■ **Poon PY.** Comparison of MRI and CT scanning in assessment of tumor response. 10th Clinical Cancer Research Conference of the Ontario Cancer Treatment and Research Foundation. Geneva Park, Lake Couchiching, Ontario, September, 1985.

■ **Poon PY (With RM Henkelman, MJ Bronskill, H Dunlap and G Ege).** MR imaging, CT and radionuclide scintigraphy in the detection of liver metastases. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Poon PY (With RM Henkelman, MJ Bronskill, H Dunlap, DF Rideout, H Shulman, MI Steinhardt, GL Weisbrod and RJ Ginsberg).** MR imaging and CT in detection of mediastinal involvement in bronchogenic carcinoma. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Poon PY (With RW McCallum, RM Henkelman, MJ Bronskill, H Dunlap, SB Sutcliffe and M Gospodarowicz).** MR imaging in the detection of extraglandular spread of prostate carcinoma. 71st Scientific Assembly and Annual Meeting of the Radiological Society of North America. Chicago, Illinois, November, 1985.

■ **Rauth AM (With TA Lapointe and MJ Weinberg).** Radiation and 5-Fluorouracil (5FU): Effects on a transplantable squamous cell tumor in mice. Radiation Research Society Meeting. Los Angeles, California, May, 1985.

■ **Rauth AM (With RS Marshall).** Modification of the cytotoxic activity of Mitomycin C. Radiation Research Society Meeting. Los Angeles, California, May, 1985.

■ **Rauth AM (With KC Agrawal, RP Gupta, MA Casey, RD Yates and S Rockwell).** Cytotoxicity, radiosensitization, pharmacokinetics and neurotoxicity studies of N-(3-pirolyl)-2-hydroxy-1-(2-nitroimidazole-1-yl) proponamide (S-193). Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Rauth AM (With RA McClelland, S Brothers, J Bolton and KR Laderoute).** Preparation and properties of 2-nitrosoimidazoles. Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Rauth AM (With R Panicucci and RA McClelland).** Stable reduction products of 2-nitrosoimidazoles. Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Rauth AM (With MJ Weinberg and TA Lapointe).** Growth delay in murine squamous cell tumors after local radiation and infusional 5-Fluorouracil treatment. Conference On Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Rideout DF.** Radiology of the head, neck and lung cancer. Cancer Update 1985. Sudbury, Ontario, October, 1985.

■ **Rideout DF.** Romancing the bone: An introduction to the use of radiology in archeology. The Aesculapian Club. Toronto, Ontario, February, 1986.

■ **Saunders CJ.** No caviar or lobster tails available but anything else goes. 27th Annual Conference of the Ontario Dietetic Association. London, Ontario, May, 1985.

■ **Saunders CJ.** Quality Assurance program: A practical perspective. Nutrition and Food Service Administration Conference. Ontario Hospital Association. Toronto, Ontario, March, 1986.

■ **Simpson WJ.** A medullary thyroid cancer screening clinic. 16th International Congress of Radiology. International Society of Radiation Oncologists. Honolulu, Hawaii, July, 1985.

■ **Simpson WJ.** Prognostic factors in differentiated thyroid cancer. 16th International Society of Radiation Oncologists. Honolulu, Hawaii, July, 1985.

■ **Simpson WJ.** Radioiodine and radiotherapy in the management of papillary and follicular thyroid cancer. 16th International Congress of Radiology. International Society of Radiatien Oncologists. Honolulu, Hawaii, July, 1985.

■ **Simpson WJ.** Panel of thyroid cancer. American Academy of Otolaryngologists, Head and Neck Surgeons. Atlanta, Georgia, October, 1985.

■ **Simpson WJ.** Management of medullary thyroid cancer. Thyroid Cancer Symposium. Saskatoon, Saskatchewan, February, 1986.

■ **Simpson WJ.** Prognostic factors, radioiodine and radiotherapy in papillary and follicular cancers. Thyroid Cancer Symposium (invited speaker). Saskatoon, Saskatchewan, February, 1986.

■ **Sinclair-Murray B.** What are clinical trials? The Institute for Social Workers in Oncology. Toronto, Ontario, October, 1985.

■ **Sutcliffe SB.** PMH experience: Clinical stage I and II Hodgkin's disease. 16th International Congress of Radiology. Honolulu, Hawaii, July, 1985.

■ **Sutcliffe SB (With PY Poon and RM Henkelman).** NMR in clinical oncology. Plenary Lecture. 16th International Congress of Radiology. Honolulu, Hawaii, July, 1985.

■ **Tannock IF.** Basic research in bladder cancer. 1st International Consensus Development Conference on Guidelines for Clinical Research in Bladder Cancer. Antwerp, Belgium, June, 1985.

■ **Tannock IF.** Experimental chemotherapy and concepts related to the cell cycle. Alma Howard Memorial Symposium. Manchester, England, July, 1985.

■ **Tannock IF.** Hormonal therapy for cancer of the prostate. American College of Surgeons Annual Meeting. Chicago, Illinois, October, 1985.

■ **Tannock IF.** Systemic therapy for prostatic cancer. Delta Inn. Mississauga, Ontario, November, 1985.

■ **Tannock IF.** Overview of medical oncology. Welland County Medical Association. Port Colbourne, Ontario, January, 1986.

■ **Tannock IF.** Xenograft and tissue culture models for human bladder cancer. Bladder Cancer: Future directions for treatment. Marco Island, Florida, February, 1986.

■ **Theriault C (With PJ Fitzpatrick).** Malignant parotid tumors. American Radium Society. San Francisco, California, April, 1986.

■ **Thomas GM.** Is radiation therapy necessary after local excision of breast cancer. Controversies in the Management of Breast Cancer Symposium. Ottawa, Ontario, April, 1985.

■ **Thomas GM.** The role of radiation in the management of all stages and extents of seminoma. The Second Germ Cell Tumour Conference. Leeds, England, April, 1985.

■ **Thomas GM.** Optimal management of stage II seminoma. American Urological Association. Atlanta, Georgia, May, 1985.

■ **Thomas GM.** Prospects in the management of cervical carcinoma. Clinical Day on Progress in Gynecologic Oncology, Sunnybrook Hospital. Toronto, Ontario, May, 1985.

■ **Thomas GM.** i) A phase I-II study of concurrent radiation, Mitomycin C and 5-Fluorouracil in squamous cell carcinoma of the cervix. ii) The role of radiation in the management of germ cell tumours in the ovary. Boorhaave Course, Leeuwenhoek Congress Centre. Noordwijkerhout, The Netherlands, June, 1985.

■ **Thomas GM.** The management of seminoma. Grand Rounds, Sutter Hospital. Sacramento, California, July, 1985.

■ **Thomas GM.** i) The results of therapy for seminoma in Ontario. ii) Optimal therapeutic management of invasive carcinoma of cervix. 16th International Congress of Radiology. Honolulu, Hawaii, July, 1985.

■ **Thomas GM.** Combined modality therapy for carcinoma of the cervix and anal canal. Aachen, Germany, November, 1985.

■ **Thomas GM.** Extended field irradiation in carcinoma of the cervix. Society of Gynecologic Oncologists. Palm Springs, California, January, 1986.

■ **Thomas GM.** i) Implications for future therapy for carcinoma of cervix. ii) The role of radiation therapy in endometrial carcinoma. iii) Radiation therapy for carcinoma of the ovary. The PMH experience. 4th Annual Cancer Symposium, Medical Center of Beaver County. Beaver Falls, Pensylvania, March, 1986.

■ **Till JE.** Stem cell biology: Quality of survival; New directions in cancer research. ICI Pharma Lecturer. Vancouver and Victoria, British Columbia, April, 1985.

■ **Till JE.** Research on quality of life. Medical Research Council 25th Anniversary Symposium. Winnipeg, Manitoba, October, 1985.

■ **Van der Vliet W.** ASCO highlights — 1985. Canadian Society of Hospital Pharmacists — PSG — Oncology. Toronto, Ontario, May, 1985.

■ **Van der Vliet W.** Pain management in the oncology patient. Student-Preceptor Workshop. Sudbury, Ontario, August, 1985.

■ **Van der Vliet W.** Pain management with focus on the cancer patient. Telemedicine for Ontario. Toronto, Ontario, October, 1985.

■ **Van der Vliet W.** Toxicity of chemotherapy and pain management. Social Service Conference. Toronto, Ontario, October, 1985.

■ **Van der Vliet W (With R Buckman and G McCoy).** The heroin debate. Fall Focus, Canadian Society of Hospital Pharmacists. Toronto, Ontario, October, 1985.

■ **Van der Vliet W (With R Buckman and F Ferris).** Pain management. Peel Memorial Hospital. Toronto, Ontario, January, 1986.

■ **Van der Vliet W.** Toxicity of antineoplastic agents. Professional Practice Conference. Toronto, Ontario, February, 1986.

■ **Van Dyk J.** Broad beam attenuation of high energy photons in lead. 14th International Conference on Medical and Biological Engineering and 7th International Conference on Medical Physics. Espoo, Finland, August, 1985.

■ **Van Dyk J.** Developments in photon beam dose calculations. Kuopio, Finland, August, 1985.

■ **Van Dyk J.** Total and half-body photon irradiation. Review of AAPM Task Force Group 29 Activities. 14th International Conference on Medical and Biological Engineering and 7th International Conference on Medical Physics. Espoo, Finland, August, 1985.

■ **Van Dyk J (With K Mah, TJ Keane and PY Poon).** Dose response data for acute radiation induced pulmonary damage: Preliminary results. AAPM Task Group 29 Activities. 14th International Conference on Medical and Biological Engineering and 7th International Conference on Medical Physics. Espoo, Finland, August, 1985.

■ **Whitmore GF.** Biological properties of reduced nitroheterocyclics. 2nd Biochemical Pharmacology Symposium on Bioreduction in the Activation of Drugs. Headington Hill Hall, Oxford, England, July, 1985.

■ **Whitmore GF.** Radiation therapy and repair genes. Symposium on Structure and Function of Cloned DNA Repair Genes. Paterson Laboratories. Manchester, England, October, 1985.

■ **Whitmore GF (With S Gulyas).** Studies on the toxicity of RSU-1069. Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Whitmore GF (With AJ Varghese).** Conjugation with thiols: A possible mechanism for the enhanced radiation sensitizing property of RSU-1069. Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Whitmore GF (With AJ Varghese).** Identification of a reactive glutathione conjugate as a metabolite of SR-2508 in CHO cells. Conference on Chemical Modifiers of Cancer Treatment. Clearwater, Florida, October, 1985.

■ **Woo MK (With JR Cunningham, DWO Rogers and A Bielajew).** An examination of the dependence of mass energy absorption coefficient ratios on depth and beam size in a phantom. 27th Annual Meeting of the American Association of Physicists in Medicine. Seattle, Washington, August, 1985.

■ **Woo MK (With CS Kwok, M Irfan and JR Cunningham).** Beta dosimetry at a tissue-bone interface. 27th Meeting of the American Association of Physicists in Medicine. Seattle, Washington, August, 1985.

■ **Yaffe MJ.** Scanned projection digital mammographic imaging. Joint Meeting of the American Roentgen Ray Society and the Society of Photographic Scientists and Engineers. Boston, Massachusetts, April, 1985.

■ **Yaffe MJ.** Research on new methods of x-ray imaging. Annual Meeting of the Canadian Association of Physicists. Fredricton, New Brunswick, June, 1985.

■ **Young SD (With RP Hill).** Metastatic behaviour of murine tumour cells recovered from micrometastas. American Association for Cancer Research, 76th Annual Meeting. Houston, Texas, May, 1985.

Donations

THE operations of The Princess Margaret Hospital, which is incorporated in The Ontario Cancer Institute, are financed similarly to those of other public hospitals in Ontario with the exception that additional funds are received from The Ontario Cancer Treatment and Research Foundation.

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ALSO, our research and clinical activities are assisted by bequests and donations to the PMH Trust. We wish to acknowledge the following bequests and donations to the PMH Trust during the past year.

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Frank Squizzato, organizer of the Canadian Computer Golf Tournament, presented a cheque for $5,900 to Johanne Ratz, Administrator of OCI/PMH, to assist with the care of patients.

Carl Peake (right), Court Trillium section of the Independent Order of Forresters, presented a cheque to Henry Jaywardena (left), Rehabilitation Medicine, for purchase of a hemiplegic wheelchair and toys for the children's waiting room.

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